Prevalence and Patterns of Medication Use in Children and Adolescents with Autism Spectrum Disorders in the Western Cape

Proposal for a thesis to meet the requirements of the Masters of Medicine in Psychiatry at the University of Cape Town.

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Declaration

This research report is based on independent work and neither the whole work nor any part of the work has been, is being, or is to be submitted for another degree to any other university. This work has not been published prior to registration for the Masters of Medicine in Psychiatry degree.

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1. Introduction

1.1. Abstract

The Autism Spectrum Disorders(ASD) are a group of neurobiological conditions of growing prevalence for which there is no known cure. International prevalence studies have determined that children and adolescents with ASD are a highly medicated population. This comes to light in the context of a paucity of data around the efficacy of commonly prescribed medications. There is no data around the prevalence of medication use in the ASD population in South Africa. The aim of this study is to determine the prevelance and patterns of medication use in children and adolescents with ASD in the Western Cape and to determine the relationship between demographic variables and behaviours and medication use. This is a cross-sectional study design; a survey questionnaire and the Nisonger Child Behaviour Rating Form (NCBRF) will be utilized to collect the relevant data. The study will be conducted at two schools for children and adolescents with ASD in Cape Town. Participants will also be recruited from the Autism Action mailing list. Participants will be parents and caregivers of children and adolescents between the ages 3 and 18 with a formal ASD diagnosis, accessing educational services and residing in the Western Cape. The survey questionnaire will collect demographic data, details of all medication currently used, the presence of any comorbid medical and psychiatric conditions and information on educational placement. The NCBRF will be used to evaluate the children's social and problem behaviours.

Hypotheses

1. The prevalence rates of the use of psychotropic medication, over the counter (OTC) preparations and special diets are high in children and adolescents with ASD in the Western Cape.
2. Higher levels of problem behaviours predict greater psychotropic medication use.
3. Increasing age predicts greater psychotropic medication use.
4. Younger age predicts greater use of special diets and OTC supplements.
5. Higher income predicts greater access to health care services and therefore greater psychotropic medication use.

1.2. Aim

To investigate the prevalence and patterns of medication use amongst children and adolescents with ASD in the Western Cape.

1.4. Objectives

1. To determine the prevalence of the use of psychotropic medications, OTC preparations and special diets in children and adolescents with ASD in the Western Cape.
2. To describe patterns of psychotropic medication, OTC preparation and special diet use; including the dose, prescriber and indications for use.
3. To determine the categories of health or other professionals prescribing medications, OTC preparations and special diets to children and adolescents with ASD.
4. To determine the relationship between behaviours and psychotropic medication use.
5. To determine the relationship between age and psychotropic medication use.
6. To determine the relationship between age and special diets and OTC medication use.
7. To determine the relationship between household income and medication use.

1.5 Background and Significance

The pervasive developmental disorders (PDD) are a group of neurobiological conditions, evident in the first few years of life, that follow a chronic course and are characterised by pervasive dysfunction in three core domains: reciprocal social interaction, communication and stereotyped behaviours (American Psychiatric Association, 2000). The DSM IV (American Psychiatric Association, 2000) defines five PDD: Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder , Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). The Autism Spectrum Disorders (ASD) include Autistic Disorder, Asperger's Disorder and PDD-NOS. These conditions show marked clinical heterogeneity with changing symptomatology relating to developmental stage (Seltzer, et al., 2003).

The prevalence rates of Autistic Disorder vary markedly between epidemiological studies. According to the DSM IV, the mean prevalence rate is 5 cases per 10 000 with a range of 2 to 20 cases per 10 000 individuals (American Psychiatric Association, 2000). Although evidence is lacking, PDD-NOS and Asperger's Disorder appear to be more common (Bernet, et al., 1999). More recent United States of American estimates predict that 3 to 6 out of every 1000 children will have autism (National Institute of Health, 2009). These figures were concordant with data from studies from multiple sites and using varying methodologies (Geschwind, 2009). The apparent rise in prevalence remains a controversial issue and may be related to improved identification, and not a true rise, in incidence (Gurney, et al., 2003). According to the statistics of Autism Western Cape, 1 in 86 South African children under the age of 6 is affected by autism and 10 children per week are being diagnosed at Red Cross, Tygerberg and Lentegeur Psychiatric Hospitals (Autism Western Cape, 2009). A 2009 review stated prevalence rates for ASD between 1 per 150 and 1 per 200 individuals and rates of 1 per 500 for the diagnosis of strictly defined autism.

There is no cure for autism, but behavioural and pharmacological interventions are aimed at reducing core symptoms, managing other problem behaviours and treating psychiatric

comorbidities. This allows for improved level of functioning and quality of life (Deokar, et al., 2008). Dysfunctional behaviours interfere with educational and rehabilitation interventions and can cause significant distress (Bernet, et al., 1999). Early identification of ASD and the implementation of sustained, appropriate educational and behavioural interventions improves long term clinical outcomes (Bernet, et al., 1999) (Tsai, 1999).

Despite the implementation of educational and behavioural interventions, many individuals remain impaired and distressed and the use of pharmacological interventions becomes necessary (Posey, et al., 2001). To date, risperidone is the only medication approved by the U.S Food and Drug Administration (FDA)for the treatment of problem behaviours, specifically irritability, aggression and self-injury, in children with autism (Food and Drug Administration, 2006). Psychotropic medications from all classes are currently in use including antidepressants, mood stabilizers, antipsychotics, antihypertensives and stimulants. Alternative and more easily obtainable over the counter (OTC) treatments such as megadose vitamins, herbal remedies and specialized diets are also used. There is minimal data about the long term safety of any of these agents (McCracken, 2005).

Medication surveys in the field of intellectual disabilities exposed elevated prescribing rates and served to guide changes in prescribing practices in the United States of America (Aman, et al., 2003). These studies did not specifically address ASD.

There have been several scientific prevalence studies since 1995 which show that the ASD population is highly medicated, and is becoming increasingly medicated (Aman, et al., 1995) (Martin, et al., 1999) (Langworthy-Lam, et al., 2002) (Aman, et al., 2003) (Witwer, et al., 2005) (Aman, et al., 2005) (Oswald, et al., 2007) (Gurney, et al., 2006) (Mandell, et al., 2008) (Esbensen, et al., 2009). This body of epidemiological data is growing in parallel with systematic reviews into evidence supporting prescribing practices in ASD. These reviews reveal an urgent need for placebo-controlled trials of commonly prescribed medications (Tsai, 1999) (Posey, et al., 2001) (King, 2000) (Bodfish, 2004)

(Palermo, et al., 2004) (Kwok, 2003) (Findling, 2005) (Leskovec, et al., 2008) (Mc Dougle, et al., 2008) (Parikh, et al., 2008).

Most available data on the prevalence of medication use in ASD comes from the United States of America. The very first medication prevalence survey was conducted by Rimland in 1988 (Rimland, 1988). This was an informal survey completed by approximately 4000 parents of autistic children. The questionnaire included parental efficacy ratings. Thioridazine was the most commonly used drug (n=724), but high dose vitamin B6 and magnesium received the highest ratings for behavioural improvement.

The first scientific study was a point prevalence survey conducted in the Autism Society of North Carolina in 1992 and 1993 (Aman, et al., 1995). The questionnaire elicited demographic and medication use information, specific data related to epilepsy, as well as parent satisfaction with treatment. Of the 838 respondents aged 1 to 82, 33.8% of the sample were taking some psychotropic drug or vitamin for autism or associated behavioural or psychiatric problems. If all agents, including vitamins, antiepileptics and other physical treatments were included, over 50% of the population were medicated. Neuroleptics were the most prevalent group (12.2%) with greater use of thioridazine than haloperidol. The next most commonly used drugs in order were: psychostimulants (6.6%), anxiolytics (6.3%), antidepresants (6.1%), antihypertensives (4.4%) and mood stabilizers (3.9%). Antiepileptic medications were considered as mood stabilizers in the absence of comorbid epilepsy. Of the sample, 19.2% were taking vitamins and 13.2% anticonvulsants. Age and type of housing (a proxy variable reflecting difficulty in management) were found to be independent predictors of psychotropic medication use.

A further two large point prevalence studies of medication use in individuals with ASD have since been conducted in questionnaire form (Aman, et al., 2003) (Langworthy-Lam, et al., 2002). The second study was done in the Autism Society of Ohio in 1999 and the third in the Autism Society of Carolina in 2001 (NC2). The three studies utilized the same questionnaire and were later compared

to assess longitudinal trends and regional effects (Aman, et al., 2005). There were significant increases in medication use with time.

In the second Northern Carolina study, of the 1538 respondents between the ages 3 and 56, 45.7% of individuals with autism were taking psychotropic drugs. This increased to 53.1% with the inclusion of vitamins and antiepileptics (Langworthy-Lam, et al., 2002). Antidepressants were the most commonly used psychotropic medication (21.7% of the sample), followed by antipsychotics (16.8%) and stimulants (13.9%). The longitudinal trend was a very large increase in antidepressant utilization with significant increases also occuring in antipsychotic, psychostimulant and anitihypertensive utilization. Changing patterns were thought to reflect increased physician prescribing of the newer selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics. The first Carolina study had been completed before the introduction of these agents. These medications have greater perceived safety as well as a growing body of evidence to support their use (Mc Dougle, et al., 2008) (Leskovec, et al., 2008). In keeping with previous findings, greater age and greater severity of autism and intellectual disablility predicted psychotropic medication use. Interestingly, younger autistic individuals had increased use of autism supplements; possibly because parents of younger indivduals seek out more “natural” remedies.

The Ohio study survey included 417 respondents aged 2 to 46 and findings were consistent with the second Northern Carolina study (Aman, et al., 2003). This went against the authors’ original hypothesis that there would be less medication use in Northern Carolina because of greater access to psychoeducational services.There was significantly greater use of supplements for autism in the Ohio group. There were strong demographic variable correlates between all three studies, with greater age and level of disability and more restrictive placement being associated with increased medication use.

Psychotropic medication has been investigated in a specific subgroup of individuals with higher functioning autism and Asperger’s disorder (Martin, et al., 1999). In addition to demographic and

medication information, data collection included developmental, behavioural and educational inventories such as the Autism Behaviour Checklist (ABC). The sample was drawn from children, adolescents and adults attending the Yale Child Study Center's Project on Social Learning Disabilites and was therefore not a naturalistic sample. Of 109 children, adolescents and adults, 55% were taking psychotropic medications with 29.3% taking more than one medication. These findings reflect similar rates to those of the general ASD population. Antidepressants were the most commonly used agents (32.1%) followed by stimulants (20.2%) and antipsychotics (16.5%). The high rate of SSRI use was again attributed to presciption practices related to limited side effect profile and the perception of the "benign" nature of these medications. An added dimension to this study was the inclusion of prescribing practices. Medications had been prescribed by general psychiatrists in 58.3% of the sample, child psychiatrists in 26.7% and by neurologists and paediatricians in 10%. There was marked clinical heterogeneity within the sample, with many symptoms that were unrelated to the core features of autism being treated pharmacologically. Of note were the high rates of depression and anxiety symptoms.

The above studies are all point prevalence studies which are reliable in extracting information about current medication use, but limited in reflecting the use of medications that are not constantly administered. This aspect was addressed in a study by Witwer and Lecavelier where information was obtained from 353 participants regarding 1 year rates and patterns of medication use (Witwer, et al., 2005). The aim of the study was to focus on the younger population with the inclusion criterion of age between 3 and 21 years. Parents also completed the Nisonger Child Behaviour Rating Form to identify problem behaviours and the Scale of Independent Behaviour-Revised, which is a standardized measure of adaptive behaviour. The one year rates of medication use were found to be similar to previous point-prevalence studies, supporting the reliability of point prevalence data. Of the subjects, 46.7% had taken at least one psychotropic medication in 1 year, 17.3% some type of vitamin and 15.5% were on a specialized diet. There is currently no empiric evidence to support vitamin use or specialized diets (Bodfish, 2004). The most prevalent medications were

psychostimulants (24%), followed by antidepressants (21.2%), antipsychotics (19.5%), alpha agonists (10.9%) and mood stabilizers (4.2%). Compared to previous studies, a higher percentage of children and adolescents were taking psychostimulants and antipsychotics. Differences in neuroleptics were accounted for by the increasing trend of atypical antipsychotic prescribing, due to mounting supportive evidence (Mc Dougle, et al., 2008). Methodological differences between the studies were also thought to contribute to the higher percentage of respondents having used antipsychotics , as children may have been given brief trials of antipsychotics over the year. Stimulant use was thought to be higher because of the nature of the age demographic of the sample. Greater age, lower adaptive skills and social competence and higher levels of problem behaviour were associated with greater medication use.

The findings of these large questionnaire based surveys are supported by evidence from recent cross-sectional telephone (Gurney, et al., 2006) and internet surveys (The Interactive Autism Network, 2008).

A limitation of surveys that utilise parental reporting is that they rely on parent recollections. Several studies have addressed this issue by altering methodological design to draw on information from various sources of medical records (Oswald, et al., 2007) (Mandell, et al., 2008). With access to large databases and without the limitation of non-response, sample sizes tend to be much larger.

Oswald and others collected data from the 2002 commercial claims and encounters databases of a healthcare information company (Oswald, et al., 2007). Their sample included all individuals under the age of 21 and information was reviewed regarding demographics, medication use as well as inpatient admissions and outpatient visits. Of the 2390 individuals with ASD, 83% had at least one drug claim in the last year from 125 medication classes. Of the sample, 57% received psychotropic or anticonvulsant medications. This finding is in keeping with point prevalence studies and supports the reliablility of the parent survey data. The most common class of psychotropic medication used was the antidepressants (32.1%) followed by, stimulants (26.9%), antipsychotics (23.5%), anticonvulsants

(15.2%), hypotensive agents (11.9%), hypnotics (5.8%) and benzodiazepines (4.2%). Antidepressants, antipsychotics and anticonvulsants showed increasing use with age. A limitation was that this study did not include over the counter drugs. Another concern, despite this being a commonly used methodology, is that data reflects what prescriptions were filled, and not whether medications were actually taken.

Mandell and others conducted a cross-sectional study of 60641 children with ASD using Medicaid claims from 2001 to determine patterns of psychotropic medication use (Mandell, et al., 2008). Medicaid is the United States Health care programme for individuals with low incomes and resources. It includes individuals with disabilities (Wikipedia, 2009). The study collected demographic data, information regarding psychotropic medication use and data on County and State characteristics. Of the sample, 56% used at least 1 psychotropic medication during 2001, with 20% of these using more than 3 concurrently. Neuroleptics were the most common (31%), followed by antidepressants (25%), stimulants (22%), mood stabilizers (21%), anxiolytics (12%) and sedatives (3%). Older children were more likely to use medication. Children in foster care had the highest rates of use of psychotropic medications. Children who had an inpatient stay were more likely to use medication. Differences were found between the ASD, with 61% of children with Asperger's disorder and PDD-NOS taking psychotropic medications and 53% of children with an Autistic disorder diagnosis taking psychotropic medications.The proportions of individuals using medications in this study could be higher than community based samples, because children accessing Medicaid may be more severely affected by autism.

To date, there has been only one longitudinal study of medication use among individuals with ASD (Esbensen, et al., 2009). Esbensen and others examined 286 adolescents (10 years or older) and adults over a 4.5 year period. Their findings confirmed the high prevalence rates of medication use and the increasing use of medication over time. Initially 70% of individuals were taking psychotropic or non psychotropic medications. This increased to 81 %, 4.5 years later. At the beginning of the

study, 57% took at least one psychotropic medication and 37% took at least one non-psychotropic medication. For both types of medication, the number of medications and the proportion of individuals taking medications increased with time. Of the nonmedicated individuals in the sample, 30% began taking medication during the study timeframe. Higher rates of medication use than those presented in previous studies can be related to the older age of the sample. Older age has already been shown to predict increasing medication use (Aman, et al., 2005). Adolescents have an increased risk of developing seizure disorder and psychiatric comorbidity which could explain greater medication use with age (American Psychiatric Association, 2000). The longitudinal increases in medication use could reflect changes in prescribing practices as discussed above. The authors conclude that more people with ASD are taking medications and that more medications are taken over time. Individuals who are medicated are likely to stay this way, the pattern being more pronounced for psychotropic medications.

The above studies use various methodologies to explore the prevalence and patterns of psychotropic use among idviduals with ASD. Despite the various methodologies, all studies report similar findings. This population is highly medicated with increasing use of medications reflecting changes in prescibing patterns. Findings from other studies support the reliability of point prevalence survey data.

Despite the growing prevelance of medication use in this population, the evidence base to support the prescribing of medications remains small. The pathogenesis of autism is not fully understood and as yet there is no cure (Kwok, 2003). First line interventions are behavioural and cognitive strategies. These include parental counselling, behaviour modification, special education techniques, sensory integration training, speech therapy, social skills training and other communication and social interventions (Tsai, 1999) (Bodfish, 2004). Applied behaviour analysis (ABA) has the most supportive evidence (Geschwind, 2009). These interventions are most powerful when initiated early on. Distressing and abberant behaviours interfere with the implementation of behavioural and

educational interventions. Medication targets distressing and abberant behaviours. This enhances the individual's ability to participate in these programmes and improves the positive response to behavioural and cognitive strategies (Tsai, 1999) (Kwok, 2003).

The core features of autism include impairments in social interactions, impaired communication skills and stereotyped patterns of behaviour, interests and activities. Other behaviour symptoms are common. According to Tsai, about 60% have poor attention and concentration; 40% are hyperactive; 43%-88% exhibit morbid or unusual preoccupation; 37% have obsessive phenomena; 16%-85% show compulsions or rituals; 50%-89% demontrate stereotyped utterances; 70% exhibit stereotyped mannerisms; 17%-74% have anxiety or fears; 9%-44% show depressive mood, irritability, agitation and inappropriate affect; 11% have sleep problems; 24 %-43 % have a history of self injury; and 8% have tics. These behaviours, which were previously thought to be associated features of autism, are now considered to be features of coexisting neuropsychiatric conditions such as attention deficit hyperactivity disorder (ADHD), affective disorders, obsessive compulsive disorder and Tourette's disorder (Tsai, 1999).

Psychiatric comorbidities are common in children with ASD with estimate prevalence rates between 25%-70% (Geschwind, 2009). A population derived cohort study found high rates of psychiatric disorders and frequently multiple disorders in children with ASD. Of the 112 participants, 70% had one disorder and 41% had 2 or more disorders. The most common diagnosis was social anxiety disorder (29,2%), followed by ADHD (28,2%) and oppositional defiant disorder (28,1%) (Simonoff, et al., 2008).

Clinical dysfunctions in other domains are common in individuals with ASD. These include sensory abnormalities, developmental regression, motor signs such as hypotonia and apraxia, gross motor delay, sleep disturbance, and gastrointestinal disturbance (Geschwind, 2009). Comorbid medical disorders are found in 10%-15% of individuals with autism (Steyn, et al., 2003).

Studies show that neurochemical factors play a role in the pathogenesis of autism. These theories provide the rationale for psychopharmacological practices. Tsai summarizes the current neurochemical data in his 1999 review .Theories exploring the role of serotonin in autism include those of hyperserotonemia, decreased serotonin binding and decreased central serotonergic responsivity. Current evidence concerning the role of dopamine in autism is mixed, but dopamine agonists have been shown to worsen preexisting stereotypies, aggression and hyperactivity. The evidence regarding norepinephrine and epinephrine is also inconclusive with some studies showing lower levels in individuals with autism. Neuropeptide studies have shown abnormalities in autistic subjects and autistic behaviours resembling opiate-induced behaviours in animals and certain behaviours seen in adult oppiate addicts (Tsai, 1999).

In a recent review, Parikh and others discuss the neurochemical underpinnings of aggressive and self injurious behaviours in individuals with autism. Several studies related to the dopaminergic and serotonergic systems as well as the noradrenergic and endogenous opioid systems are cited (Parikh, et al., 2008).

There have been a number of reviews in the past decade concerning the evidence base supporting prescribing practices in individuals with autism. Out of this body of literature the findings of the most recent review by Leskovec and others in 2008 will be discussed here. The overall conclusion is the same as that of previous reivews; there are several medications that have been identified as possibly being effective in treating autism, but additional clinical trials are much needed (Leskovec, et al., 2008). This review summarizes the evidence under several behavioural headings which will be used in the discussion below.

Under **ADHD like symptoms** evidence is cited for the use of the psychostimulant methylphenidate. This includes a large, double blind placebo control study by the Research Units on Paediatric Psychopharmacology (RUPP). Methylphenidate was shown to be efficous but with reduced effectiveness and a less satisfactory side effect profile. There is currently insufficient evidence to

support the use of amphetamines or atomoxetine. There is some evidence for the use of tricyclic antidepressants, but major concerns regarding tolerability and cardiac toxicity will limit further studies. Further research is indicated for other antidepressants, venlafaxine and bupropion. Future research is also recommended for the alpha-2 adrenergic agonists, clonidine and guanfacin and the Alzheimer's disease therapeutics, donepezil, galantamine and memantine before they can be safely recommended.

Aggression, irritability, and self-injurious behaviours are identified as being very disruptive in individuals with ASD.There is reasonable evidence, including 3 double-blind, placebo-controlled cross-over trials, for the typical antipsychotic haloperidol. Despite this, the high risk of developing extrapyramidal side effects make haloperidol and other typical antipscyhotics a less favourable choice when compared to the atypical antipshychotics. Clozapine may have a role in treatment resistant cases, but there are concerns about the side effect profile and the need for haematological monitoring. Risperidone has been extensively studied and approved by the FDA for the treatment of irrritability and aggression. The authors do caution that continued research is needed regarding the long term effects. There is limited evidence regarding olanzapine as well as on going concern about the propensity for weight gain on this agent. Studies with quetiapine show marked adverse events with minimal effectiveness and it is not recommended as first line treatment. There is some promising evidence for ziprasidone and aripaprazole but further studies are needed. In another recent review on atypical antipsychotics use in children and adolescents with autism by McDougle, the atypicals are identified as the emerging firstline management for irritability (Mc Dougle, et al., 2008). Other agents are also considered in the Leskovec review, but before their use can be advocated for aggression and irritability, further studies are recommended. These include the anitepileptics topiramate and divalproex sodium as well as the beta-blockers and buspirone.

Stereotypy and repetitive behaviours are identified as being common in individuals with ASD and the impairments comparable to the obsessions and compulsions found in patients with obsessive-

compulsive disorder. The SSRIs are used for the treatment of OCD and have therefore been the focus of several studies. The SSRI fluoxentine demonstrated improvement in open-label trials, but control trials are warranted. Fluvoxamine is well tolerated and it appears to be more effective in older patients. Sertraline lacks evidence from randomized control studies and studies involving children. Paroxetine has been shown to be well tolerated but also evidence from randomized control studies is lacking. At the time of this review, citalopram had not been well studied. A recent double blind randomized control trial by King and others found citalopram to be ineffective for the treatment of repetitive behaviours in children and adolescents with ASD (King, et al., 2009). This trial utilized the methodology much needed in medication trials for individuals with ASD. Clomipramine has been associated with serious side effects in studies and its use cannot be recommended.

There is limited evidence in this review for the pharmacological treatment of **deficits in social behaviours.** Further studies are recommended for D-cycloserine, a partial agonist at the N-methyl-A-apartate glutamate receptor subtype and the cofactor tetrohydrobiopterin. Evidence did not support the use of naltrexone the opiate blocker, or the more alternative biological treatments such as secretin (a peptide hormone that stimulates pancreatic secretion), vitamins or nutritional supplements.

As stated, the conclusion of this review highlights the fact that medication is being prescribed in the absence of sound evidence and that further trials like the recent citalopram trial are much needed.

To my knowledge, there is no evidence regarding the prevalence and pattern of medication use in children with ASD within the South African context. Our unique demographic and social environment may reflect patterns that are not in keeping with international trends. This knowledge is vital to inform clinical practice and guide future research.

2. Methods

2.1. Sampling

The sample for this study will be drawn from two schools for children and adolescents with ASD in Cape Town and the database of Autism Action South Africa an organization created by parents to serve and support anyone who has daily contact with an ASD person.

Alpha and Vera schools fall under the administration of the Western Cape Department of Education. All learners have a formal diagnosis of ASD.

Alpha school is located in Woodstock, but a transport service collects children throughout Cape Town. There are currently over 60 learners between the ages 4 and 18 attending the school. Children who present to the school have a provisional diagnosis of ASD from a doctor. They undergo a formal 3 week observation process by a multidisciplinary team. The team consists of a psychologist, teacher, speech therapist and occupational therapist. The formal diagnosis of an ASD is then given based on the DSM IV criteria (American Psychiatric Association, 2000) and the Childhood Autism Rating Scale.

Vera School is situated in Rondebosch East. There are currently 97 learners attending the school. There is a hostel which houses 30 children who cannot attend as day scholars because of transport difficulties or behavioural problems. All children have a formal diagnosis of ASD made using the DSM IV criteria. Children from throughout the Western Cape attend the school.

Drawing from a school based sample ensures that children have a formal ASD diagnosis and improves response rate. Teachers can also assist parents with literacy problems to complete the form which will minimize reporting bias. A limitation of drawing the sample exclusively from the schools, is the small size. Therefore, participants will also be recruited from Western Cape members of the Autism Action database. This will not only increase sample size, but also access children who are attending main stream schools.

Autism Action South Africa is an independent organisation. There are currently 300 registered members, the majority of whom reside in the Western Cape. All children have a formal ASD diagnosis.

Inclusion criteria for the study will be a formal ASD diagnosis, an age range between 3 and 18 years and that the child be attending an educational service and residing in the Western Cape.

2.2. Measures

2.2.1. Demographic questionnaire

Demographic and treament information will be obtained using a questionnaire. See Appendix 1. The questionnaire will be available in English and Afrikaans.

The questionnaire has been been adapted, with permission from author Dr Michael Aman, from that used in previous point-prevalence studies (Aman, et al., 2003) (Aman, et al., 1995) (Langworthy-Lam, et al., 2002). See Appendix 2.

The questionnaire consist of four sections demographics, medications, comorbid medical and psychiatric illnesses and educational information. Demographic questions include age, gender, race, current grade and total gross monthly household income. Parents will be asked to list all medications currently being used, including vitamins, over the counter preparations and any special diets. Previous studies that reviewed medication use over the previous year did not show different findings to point prevalence studies (Witwer, et al., 2005). Asking about current use will improve the accuracy of parental reporting. The dose, who prescribed the medication and indication for treatment will be included. Prescriber information is relevant in the South African context where access to health care providers remains inequitable and there is a shortage of specialists. Other general medical illnessess and psychiatric comorbidities will be asked about. The presence of epilepsy and current medication used for seizure control will be specifically asked about to ensure that anticonvulsants used for epilepsy are not included as mood stabilizers. There will be questions

on the type of educational placement because respondents from the Autism Action database may be attending a variety of educational placements. The level of intellectual disability and severity of autism has been excluded from the questionnaire because of parental under reporting found in previous studies (Aman, et al., 1995).

2.2.2. Nisonger Child Behaviour Rating Form

Parents of particpants will also be asked to complete the Nisonger Child Behaviour Rating Form (NCBRF). See Appendix 3. This is a standardized intrument for assessing behaviour in children and adolescents with intellectual and developmental disabilities (Research Unit on Pediatric Psychopharmacology at the Nisonger Center, 2008). The version designed for completion by parents will be used. It does not require an interview or observation by an interviewer. The NCBRF has been well validated in the United States and the subscales correspond highly with those of the Autism Behaviour Checklist (Aman, et al., 1996) (Tasse, et al., 1996). As instructed by the Research Unit on Paediatric Psychopharmacology (RUPP), the form will be copied onto blue paper for distribution. The NCBRF has 10 social competence items. These are rated on a four-point Likert scale ranging from [0] not true to [3] completely or always true. Scoring is distributed on two subscales, Compliant/Calm and Adaptive/ Social. The problem behaviour section consists of 66 items. These are rated on a Likert Scale from [0] if the behaviour did not occur or was not a problem to [3] if the behaviour occurred a lot or was a severe problem. The items are distributed on 6 subscales: Conduct Problem, Insecure/ Anxious, Hyperactive, Self-Injury/ Stereotypic, Self-Isolated/ Ritualistic and Overly Sensitive. The NCBRF has been translated into Afrikaans and it has been linguistically validated by the MAPI Institute (MAPI Institute, 2009). See Appendix 4. The author Dr Aman has given permission for the use of the translated version. The schools have agreed to assist parents with literacy problems to complete the form.

An envelope containing an information page (see Appendix 5), consent form (see Appendix 6), questionnaire and NCBRF survey will be sent home with all learners at Alpha and Vera schools for

completion by a parent or guardian. Parents or guardians will then return the forms in confidential envelops to the schools. The completed consent form, questionnaire and NCBRF will be collected from the schools.

Parents from the Autism Action database will be emailed with information about the study and be invited to participate. Interested parents will email the investigators. Parents whose children are attending the schools will be asked not to fill out two separate surveys and to rather complete the one sent out from the school. Parents who are willing to participate will be posted the information page, consent form, questionnaire and NCBRF. In order to ensure that participants are residing in the Western Cape, the survey will only be posted to parents who can provide a postal address within the Western Cape. Completed forms can then be posted back to the investigators.

2.3. Data analysis

Point prevalence of medication will be determined using frequency counts. If epilepsy is not present, anitconvulsants will be grouped as mood stabilizers along with lithium.

In order to address the hypotheses of this study, medication prevalence will be compared for age, household income and the presence of problem behaviours, as identified by subscales on the NCBRF. Age will be divided into four ranges; 3-6 years, 7-9 years, 10-12 years and 13-18 years. The average monthly household income in South Africa is R 4 415 (Eighty20). Household income will be divided into six ranges; R0-R500, R501-R2 500, R2 501-R6 000, R6 001- R16 000, R16 001- R30 000, >R 30 001. Categorical variables will be compared using Chi squared tests.

Any significant difference in prevalence of medication use for the various behaviour subscales of the NCBFR will be calculated with the Wilcoxon sum rank test.

In keeping with other studies, there is a possibility of there being associations between subject variables. For example, increasing age may be associated with increased reporting of problem behaviours due to developmental stage or the increase in size of the child. Logistic regression, a

multivariate analysis, would therefore be used to assess the significance of the relationships between these variables. Age and the NCBRF subscales will be entered as predictors in logistic regressions as continuous variables. The categorical variable gender, will be treated as a dummy variable. Stepwise logistic regression analyses will be conducted with the major drug groups as the dependent variable (i.e., drug present versus absent). At each step of the analysis, a new variable will be retained if it predicted drug status at the $p<0.05$ level (chi sqared). This will indicate a significant contribution above variables already in the model.

A statistician will be consulted when conducting the data analyses and the appropriate software will be utilized.

3. Ethical Considerations

The survey package includes an information page explaining the purpose of the survey and ensuring confidentiality. See Appendix 5. Parents will receive information about the aim and objectives of the study and be invited to participate. Participation will be entirely voluntary and participants will not be prejudiced in any way if they choose not to participate or if they withdraw consent at a later stage. Parents will be asked for their consent to use the information provided for study purposes. They will be asked to sign a consent form after they have read and understood the information page. See Appendix 6. The choice to use medication is a personal one for each family and can be a sensitive issue. Confidentiality of all study participants will be maintained. Consent can be withdrawn at any time.

The study will not be obtaining assent from children under the age of 18, as there will be no direct work with children.

Children who are 18 years old are legally able to give consent; however those with ASD may have learning and communication difficulties that interfere with their ability to give fully informed consent. Parents of children who are 18 years old will be functioning as legal guardians and they will

be asked to give consent on behalf of their children. If the parent feels that their child is able to understand the information sheet the child will be asked to sign an assent form giving persmission to use the information about them for study purposes.

Permission to conduct the survey will be obtained from the principals of both schools and the Board of Autism Action South Africa.

Permission to conduct the survey at the schools will be obtained from the Western Cape Department of Education.

The full research protocol will be submitted to the Departmental Research Committee and permission will be obtained from the University of Cape Town (UCT) Ethics Committee. The protocol and ethics approval will then be submitted to the post graduate committtee for approval by the Faculty of Health Sciences.

The findings of the research project will be made available to the schools and a presentation of the findings will be done for all parents, teachers and interested parties.

This study adheres to the principles of the Declaration of Helsinki (World Medical Association, 2008).

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5. Appendices

5.1. Appendix 1: Survey Questionnaire

Prevalence and Patterns of Medication Use in Children and Adolescents with Autism Spectrum Disorders in the Western Cape Questionnaire

Please answer as many questions as you can.

1. Identification Data

a) Name of individual with autism: _____

b) Date of Birth of individual with autism: _____Day _____Month _____Year

c) Sex of individual with autism(tick): Male_____ Female_____

d) Ethnicity of individual with autism (tick): Asian___ Black African___ Coloured ___ Indian ___ White ___ Other_____

e) Relationship of person completing this form to individual with autism (parent, guardian):
_____

f) Total gross (before tax deductions) monthly household income (tick):
R0-R500___ R501-R2 500____ R2 501-R6 000____ R6 001-R16 999___ R16 001-R30 000__ R30 000+ ___

2. Medicines

a) Please list all medications, vitamins and supplements **CURRENTLY TAKEN** by your child in the table below:

- If no medication is taken, please print "N/A".
- If medication is taken "Only When Needed", please print "As Needed" under the "Dosage" column.
- Please include who prescribed the medication e.g. General Practitioner, Psychiatrist, Paediatrician, Neurologist.
- Please include purpose for which the medication was prescribed e.g. sleep difficulties, problem behavior, ADHD.
- Please include any vitamins, supplements or over the counter medications as well.
- If you don't know the answer to a particular question, just write "don't know" and move on to the next question.

Name of Medication or Supplement	Dose per day (mg)	Year Started	Prescriber	Indication

b) Does your child experience any side effects (unwanted effects) from these medications?
Yes____ No____
If yes, please mention what the side effect(s) are and which medication(s) cause them below:
_____
_____
_____
_____

c) Is your child on any special diet for autism?
Yes____ No____
If yes, what diet and who recommended the diet?
_____
_____

3. Other Illnesses

a) Does your child have any health conditions (asthma, diabetes)? Please list below.
_____
_____
_____

b) Has your child been assessed as having a psychiatric or behavioural diagnosis (ADHD, depression)? Please list below.
_____
_____
_____

c) Does your child have epilepsy (fits, seizures)?
Yes___ No____
If yes, please list medications used for seizures below.
_____
_____
_____

4. Information on Education

a) Does your child attend one of the following education placements?
(Please tick any that presently apply)

__ (I) Regular class in regular school (may include some special provisions in class)

__ (II) Special class in regular school (may include those in mainstreaming activities)

__ (III) Special school

5.2. Appendix 2: Aman Survey Form

Survey of Medications in Individuals with Autism

Please answer as many questions as you can. If you don't know the answer to a particular question, just write "don't know" and move on to the next question.

1. Identification Data

a) Name of individual with autism: _____

(First) (Last)

b) Date of Birth: _____month _____day _____year

c) Sex (check): ___male ___female

d) Ethnicity: ___ African American ___ Caucasian

____Asian ___Hispanic ___Other:_____

e) Individual's weight if known: _____ pounds

f) Relation of person completing this form to individual with autism (parent, guardian, brother or sister, aunt, etc.): _____

g) Today's date: _____month _____day _____year

2. *Medicines*

a) **Please list all medications PRESENTLY TAKEN by this individual on the lines provided at the bottom of this page.** If no medication is taken, please print "N/A". If medication is taken "Only When Needed", please print "As Needed" under the "Dosage"column.
If this person is taking any supplements such as vitamins or minerals, on a regular basis, be sure to include them as well.

b) In addition, please indicate how satisfied you are with each medication using the following code:

1 = very satisfied
2 = somewhat satisfied
3 = somewhat dissatisfied
4 = very dissatisfied

Name of Medication, Vitamin, etc.	**Dosage per day (mg)**	**Year Started**	**Satisfaction (1-4)**
(1)			
(2)			
(3)			
(4)			
(5)			

(6)_____
(7)_____

c) Does this person experience any side effects (unwanted effects) from these medications? If so, please mention what the side effect(s) are and which medication(s) cause them below.

_____
_____
_____
_____
_____

3. ***Information on Seizures, if Relevant:***

Some people with autism have epilepsy (also called fits, spells, or seizures).

a) Does this individual have a seizure disorder (epilepsy)? (Please check) __yes __no

b) Does this person take any medication (for example, Depakene, Dilantin, Klonopin, Lamictal, Mysoline, Neurontin, phenobarbital, Tegretol, Zarontin) for control of seizures? (please check)

____yes ____no **(if no, skip to question 4)**

If yes, please answer the following questions:

c) How old was the person when the first seizure occurred?

_____years

d) Current frequency of seizures (please check only one):

- ❑ Still has more than a seizure a month
- ❑ Has had more than 3 seizures in the last year, but fewer than one a month
- ❑ Still has seizures, but fewer than 3 in the last year
- ❑ None in the last year
- ❑ None in the last two years
- ❑ None in the last 3 or more years
- ❑ No seizures have ever been observed

e) Has an EEG ("brain wave") and/or CAT scan ever been done for this person? (Please check)
_____yes _____no _____ uncertain

If yes, was the EEG: _____normal _____abnormal _____ don't know

was the CAT scan: _____normal _____abnormal _____don't know

f) Have you ever been told what type of epilepsy this individual has?

Examples: grand mal

Lennox Gastaut syndrome

petit mal (absence)

febrile seizure (seizure with fever)

temporal-lobe (complex partial) seizure

etc. (if so, please list below)

____yes ____no _____don't know

If yes, please list: _____

4. *Could you specify the degree of autism this individual has?*

___ mild

___ moderate

___ severe/profound

___ don't know

5. *Does this individual have mental retardation, and if so, what is its severity?*

___ no mental retardation

___ mild

___ moderate

___ severe/profound

___ don't know

6. ***Other Medical/Diagnostic Information***

a) Does this individual have medical or other problems (other than epilepsy)?

____ yes ____ no

If yes, please specify: _____

_____
_____
_____

7. ***Information on Education and Work***

a) Is this individual attending one of the following education or work placements?

(Please check any that presently apply)

__ (I) Regular class in regular school (may include some special provisions in class)

__ (II) Special class in regular school (may include those in mainstreaming activities)

__ (III) Special school

__ (IV) Work **(if so, please check the most relevant below):**

__ sheltered workshop

__ supported employment

__ employed by the community

__ other _____

__ (V) Other (please list) _____

_____

b) Is this placement specifically designed for individuals with autism? ___yes ___no

8. ***Housing Arrangements***

a) What are his/her current living arrangements? (please check one)

__ living with family (including adoptive or foster parents)

__ living independently

__ living in partially sheltered situation (e.g., supported living, group home)

__ living in sheltered environment (e.g., nursing home or institution)

__ other (please describe) _____

9. ***Parents' Education (Please circle)***

Mother	Father
a	a
b	b
c	c
d	d
e	e
f	f

a. High school not completed
b. Graduated from high school
c. Technical school, qualification obtained
d. Attended college, did not graduate
e. Graduated from college
f. Graduate or professional degree (e.g., law)

Thank you for taking part in this study! When finished, please use the envelope provided and return the questionnaire. If the envelope gets lost, please mail to:

Michael Aman, Ph.D.

The Nisonger Center

The Ohio State University

1581 Dodd Drive

Columbus, OH 43210-1296

5.3. Appendix 3: Nisonger Child Behaviour Rating Form Parent Version English

THE NISONGER CHILD BEHAVIOR RATING FORM

PARENT VERSION

Child's Name: _____ Child's Date of Birth: ____/____/____
month day year

Rater's Name: _____ Date of Rating: ____/____/____
month day year

Relation of Rater to Child: • parent [1] • other [9]: _____
(please specify)

I. Please describe any special circumstances or mediating factors that may have affected the child's behavior in the recent past (the last month or two) or prevented you from making complete ratings.

II. **POSITIVE SOCIAL.** Please describe the child's behavior as it was at home over the last month.

	IN THE LAST MONTH, THIS CHILD HAS:	Not True [0]	Somewhat or Sometimes True [1]	Very or Often True [2]	Completely or Always True [3]
1.	Accepted redirection	•	•	•	•
2.	Expressed ideas clearly	•	•	•	•
3.	Followed rules	•	•	•	•
4.	Initiated positive interactions	•	•	•	•
5.	Participated in group activities	•	•	•	•
6.	Resisted provocation, was tolerant	•	•	•	•
7.	Shared with or helped others	•	•	•	•
8.	Stayed on task	•	•	•	•
9.	Was cheerful or happy	•	•	•	•
10.	Was patient, able to delay	•	•	•	•

III. **PROBLEM BEHAVIOR.** For each item that describes the child's behavior as it was over the last month, circle the:

0.... if the behavior **did not** occur or **was not a problem**
1.... if the behavior occurred **occasionally** or was a **mild problem**
2.... if the behavior occurred **quite often** or was a **moderate problem**
3.... if the behavior occurred **a lot** or was a **severe problem**

For each problem that occurred, circle only the score that best describes the behavior.

PLEASE DO NOT SKIP ANY QUESTIONS. IF YOU DO NOT KNOW THE ANSWER OR HAVE NOT HAD A CHANCE TO OBSERVE THE CHILD FOR A GIVEN TIME, CIRCLE THE ZERO.

1. Apathetic or unmotivated	0	1	2	3
2. Argues with parents, teachers, or other adults	0	1	2	3
3. Clings to adults, too dependent	0	1	2	3
4. Cruelty or meanness to others	0	1	2	3
5. Crying, tearful episodes	0	1	2	3
6. Hits or slaps own head, neck, hands, or other body parts	0	1	2	3
7. Defiant, challenges adult authority	0	1	2	3
8. Knowingly destroys property	0	1	2	3
9. Difficulty concentrating	0	1	2	3
10. Disobedient	0	1	2	3
11. Rocks body or head back and forth repetitively	0	1	2	3
12. Doesn't feel guilty after misbehaving	0	1	2	3
13. Easily distracted	0	1	2	3
14. Easily frustrated	0	1	2	3
15. Overly sensitive; feelings easily hurt	0	1	2	3
16. Exaggerates abilities or achievements	0	1	2	3
17. Explosive, easily angered	0	1	2	3
18. Has rituals such as head rolling or floor pacing	0	1	2	3
19. Fails to finish things he/she starts	0	1	2	3
20. Feelings easily hurt	0	1	2	3
21. Feels others are against him/her	0	1	2	3
22. Harms self by scratching skin or pulling hair	0	1	2	3
23. Feels worthless or inferior	0	1	2	3
24. Fidgets, wiggles, or squirms	0	1	2	3
25. Shy around others; bashful	0	1	2	3
26. Gets in physical fights	0	1	2	3
27. Irritable	0	1	2	3
28. Repeatedly flaps or waves hands, fingers or objects (such as pieces of string)	0	1	2	3
29. Isolates self from others	0	1	2	3
30. Lying or cheating	0	1	2	3
31. Nervous or tense	0	1	2	3
32. Gouges self, puts things in ears, nose, etc., or eats inedible things	0	1	2	3
33. Overactive, doesn't sit still	0	1	2	3
34. Overly anxious to please others	0	1	2	3
35. Overly excited, exuberant	0	1	2	3
36. Physically attacks people	0	1	2	3
37. Refuses to talk	0	1	2	3
38. Repeats the same sound, word, or phrase over and over	0	1	2	3
39. Restless, high energy level	0	1	2	3
40. Runs away from adults, teachers, or other authority figures	0	1	2	3
41. Says no one likes him/her	0	1	2	3
42. Secretive, keeps things to self	0	1	2	3
43. Repeatedly bites self hard enough to leave tooth marks or break skin	0	1	2	3
44. Self-conscious or easily embarrassed	0	1	2	3
45. Shifts rapidly from topic to topic when talking	0	1	2	3
46. Short attention span	0	1	2	3
47. Shy or timid behavior	0	1	2	3
48. Steals	0	1	2	3
49. Odd repetitive behaviors (e.g., stares, grimaces, rigid postures)	0	1	2	3
50. Stubborn, has to do things own way	0	1	2	3
51. Sudden changes in mood	0	1	2	3
52. Sulks, is silent and moody	0	1	2	3
53. Physically harms or hurts self on purpose	0	1	2	3
54. Talks back to teacher, parents, or other adults	0	1	2	3
55. Talks too much or too loud	0	1	2	3
56. Temper tantrums	0	1	2	3
57. Threatens people	0	1	2	3
58. Threatens to harm self	0	1	2	3
59. Engages in meaningless, repetitive body movements	0	1	2	3
60. Too fearful or anxious	0	1	2	3
61. Underactive, slow	0	1	2	3
62. Unhappy or sad	0	1	2	3
63. Violates rules	0	1	2	3
64. Withdrawn, uninvolved with others	0	1	2	3
65. Worrying	0	1	2	3
66. Argues with other children or peers	0	1	2	3

Developed by M. G. Aman, M. J. Tassé, J. Rojahn, and D. Hammer, 1995.

5.4. Appendix 4: Nisonger Child Behaviour Rating Form Parent Version Afrikaans Translation

DIE NISONGER KIND GEDRAGSVRAELYS

OUER SE UITLEG

Naam van kind:..... Geboortedatum van kind: ...../...../.....
Dag Maand Jaar

Naam van die persoon wat die vraelys voltooi: Datum van evaluering: ...../...../.....
..... Dag Maand Jaar

Verwantskap tussen evalueerder en kind: ❒ ouer [1] ❒ ander [9]:.....
(Spesifiseer asseblief)

I. Beskryf asseblief enige spesiale omstandighede of indirekte faktore wat die kind se gedrag mag beïnvloed het in die onlangse verlede (die afgelope maand of twee), of wat u mag verhoed om volledige evaluerings te maak

II. **SOSIALE VERWANTSKAPPE.** Beskryf asseblief die kind se gedrag soos dit by die huis was oor die afgelope 4 weke.

HIERDIE KIND HET, GEDURENDE DIE AFGELOPE 4 WEKE:	Nie Waar nie [0]	Ietwat of Soms waar [1]	Baie of Dikwels Waar [2]	Heeltemal of Altyd Waar [3]
1. Nuwe instruksies aanvaar	❒	❒	❒	❒
2. Idees duidelik uitgedruk	❒	❒	❒	❒
3. Reëls nagekom	❒	❒	❒	❒
4. Positiewe interaksies aan die gang gesit	❒	❒	❒	❒
5. Aan groepsaktiwiteite deelgeneem	❒	❒	❒	❒
6. Provokasie weerstaan, was verdraagsaam	❒	❒	❒	❒
7. Met andere gedeel of andere gehelp	❒	❒	❒	❒
8. Met take volgehou	❒	❒	❒	❒
9. Was opgeruimd of gelukkig	❒	❒	❒	❒
10. Was geduldig, in staat om uit te stel	❒	❒	❒	❒

(BLAAI OM)

III. **PROBLEEMGEDRAG.** Vir elke item wat die kind se gedrag beskryf soos dit oor die afgelope 4 weke was, omkring die:

> 0 .... indien die gedrag **nie** voorgekom het nie of **nie 'n probleem was nie**
> 1 .... indien die gedrag **soms** voorgekom het of **'n geringe probleem** was
> 2 .... indien die gedrag **heel** dikwels voorgekom het of **'n matige probleem** was
> 3 .... indien die gedrag **baie** voorgekom het of **'n ernstige probleem** was

Vir elke probleem wat voorgekom het, omkring slegs die telling wat die gedrag die beste beskryf.

MOET ASSEBLIEF NIE ENIGE VRAE OORSLAAN NIE. INDIEN U NIE DIE ANTWOORD KEN, OF NIE KANS GEHAD HET OM DIE KIND GEDUURENDE 'N BEPAALDE TYD WAAR TE NEEM NIE, OMKRING DIE NUL.

1.	Onbelangstellend of ongemotiveerd	0	1	2	3
2.	Stry met ouers, onderwysers, of ander volwassenes	0	1	2	3
3.	Kleef aan volwassenes, te afhanklik	0	1	2	3
4.	Wreedheid of gemeenheid teenoor andere	0	1	2	3
5.	Huilerig, tranerige episodes	0	1	2	3
6.	Slaan of klap eie kop, nek, hande, of ander liggaamsdele	0	1	2	3
7.	Uitdagend, daag volwasse gesag uit	0	1	2	3
8.	Vernietig eiendom bewustelik	0	1	2	3
9.	Konsentreer met moeite	0	1	2	3
10.	Ongehoorsaam	0	1	2	3
11.	Wieg liggaam of kop herhaaldelik heen en weer.	0	1	2	3
12.	Voel nie skuldig na wangedrag nie	0	1	2	3
13.	Maklik afgelei	0	1	2	3
14.	Maklik gefrustreerd	0	1	2	3
15.	Oorsensitief; gevoelens maklik seer gemaak	0	1	2	3
16.	Oordryf vermoëns of prestasies	0	1	2	3
17.	Plofbaar, word maklik kwaad gemaak	0	1	2	3
18.	Het rituele soos kop rol of stap die vloer op en af	0	1	2	3
19.	Kan nie dinge afhandel wat hy/sy begin het nie	0	1	2	3
20.	Gevoelens maklik seer gemaak	0	1	2	3
21.	Voel dat andere teen hom/haar is	0	1	2	3
22.	Beseer homself/haarself deur vel te krap of hare te trek	0	1	2	3
23.	Voel waardeloos of minderwaardig	0	1	2	3
24.	Vroetel, wikkel of skommel	0	1	2	3
25.	Skaam tussen andere, selfbewus	0	1	2	3
26.	Raak betrokke in fisieke gevegte	0	1	2	3
27.	Prikkelbaar	0	1	2	3
28.	Klap of waai hande, vingers of klein dinge herhaaldelik	0	1	2	3
29.	Isoleer self van andere	0	1	2	3

30.	Lieg of verneuk	0	1	2	3
31.	Senuweeagtig of gespanne	0	1	2	3
32.	Steek homself/haarself, plaas dinge in ore, neus, ens., of eet oneetbare dinge.	0	1	2	3
33.	Ooraktief, sit nie stil nie	0	1	2	3
34.	Oorangstig om mense genoeë te verskaf	0	1	2	3
35.	Ooropgewonde, uitbundig	0	1	2	3
36.	Val mense fisiek aan	0	1	2	3
37.	Weier om te praat	0	1	2	3
38.	Herhaal dieselfde klank, woord, of sinsnede oor en oor	0	1	2	3
39.	Rusteloos, hoë energievlak	0	1	2	3
40.	Hardloop van volwassenes, onderwysers, of ander gesagsfigure af weg	0	1	2	3
41.	Sê dat niemand van hom/haar hou nie	0	1	2	3
42.	Geheimsinnig, hou dinge vir homself/haarself	0	1	2	3
43.	Byt homself/haarself herhaaldelik hard genoeg om tandmerke te los of om die vel stukkend te byt	0	1	2	3
44.	Selfbewus of word maklik skaam	0	1	2	3
45.	Skuif vinnig van onderwerp tot onderwerp terwyl hy/sy praat	0	1	2	3
46.	Gee aandag vir net 'n kort tyd	0	1	2	3
47.	Skaam of vreesagtige gedrag	0	1	2	3
48.	Steel	0	1	2	3
49.	Eienaardige herhalende gedrag (bv. Staar, gryns, rigiede houding)	0	1	2	3
50.	Hardkoppig, moet dinge op eie manier doen	0	1	2	3
51.	Skielike verandering in bui	0	1	2	3
52.	Nukkerig, is stil en buierig	0	1	2	3
53.	Skaad of beseer self fisiek opsetlik	0	1	2	3
54.	Praat terug teen onderwyser, ouers of ander volwassenes	0	1	2	3
55.	Praat te veel of te hard	0	1	2	3
56.	Woedebuie	0	1	2	3
57.	Dreig mense	0	1	2	3
58.	Dreig om self te beseer	0	1	2	3
59.	Betrokke in doellose, herhalende liggaamsbewegings	0	1	2	3
60.	Te bang of angstig	0	1	2	3
61.	Onderaktief, stadig	0	1	2	3
62.	Ongelukkig of treurig	0	1	2	3
63.	Oortree reëls	0	1	2	3
64.	Teruggetrokke, onbetrokke by andere	0	1	2	3
65.	Bekommerd	0	1	2	3
66.	Stry met ander kinders	0	1	2	3

Ontwikkel deur M. G. Aman, M. J. Tassé, J. Rojahn, and D. Hammer, 1995.

5.5. Appendix 5: Participant Information Sheet

Prevalence and Patterns of Medication Use in Children and Adolescents with Autism Spectrum Disorders in the Western Cape Information Sheet

Dear Parent/Guardian,

Thank-you for participating in this survey of medication use. There have been several studies in the United States of America exploring the prevalence and patterns of medication use in the autistic spectrum disorder population. There have been no studies to date in the South African context. The aim of this study is to look at the prevalence and patterns of medication use in children and adolescents with autism spectrum disorders in the Western Cape. The study will also look at what variables affect medication use, such as age and behavioural problems. Medication includes those prescribed by a doctor as well as over the counter preparations, vitamins, supplements and special diets. The information gained in this study will help to inform prescribing practices as well as to guide further research into the field of autism.

In order to be included in the study your child must:

- Be between the ages of 3 and 18 years.
- Be living in the Western Cape.
- Have a formal diagnosis of an autism spectrum disorder made by a doctor or psychologist. Autistic spectrum disorders include Autistic Disorder, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified.
- Be attending an educational placement.

This survey consists of two parts. The first is a two page **questionnaire** that must be filled out by a parent or guardian. There are questions about demographics, medications used, other medical and psychiatric conditions and educational placement. This questionnaire has been adapted with the permission from author Dr Michael Aman from that used in American studies. The second part is a two page **checklist** specially designed to identify problem behaviours in children with developmental disorders. The check list must be completed by a parent or guardian.

Please follow the instructions carefully when completing the questionnaire and check list. It should take roughly 30 minutes to complete both parts of the survey. If your child is attending Alpha or Vera schools, your child's teacher can help you to complete the forms if there are any difficulties. If you have gained access to the survey through Autism Action, please email the investigators if you have any concerns regarding the survey (medicationsurvey@gmail.com). Please complete one survey per child. If you have received a survey through Alpha or Vera schools as well as through Autism Action, please complete and return the school survey only. Do not complete two surveys.

The information you provide will remain confidential at all times. Your child's name will not be used when reporting the findings. No one outside of the investigators will be allowed access to the information you have provided. In any future presentations or publications your child's name will not be used. On completion, the findings from the study will be presented to all interested parties. You will be able to access the findings.

Your participation in this survey is entirely voluntary. Should you chose not to participate or to withdraw from the survey at a later stage you will not be prejudiced in any way. If you choose to

participate in this study, there will be no direct benefit to you; however the information we obtain from this study will give a better understanding of the use of medications and supplements in children with Autism Spectrum Disorders in the Western Cape. This is only a survey so there is nothing painful or dangerous about participation; however you will be asked questions about your child's health and about money which may be very personal. Some people may find it difficult to discuss these matters.

Once you have read and understood this information sheet, please sign the consent form giving permission to use the information you have provided for the purpose of this study. If your child is 18 years old and you feel they are able to understand this information sheet, please ask for their permission to use the information provided about them for the study. If they agree they must sign the assent form provided.

Please return the completed forms including the signed consent form to the school in the confidential envelope provided. If you have accessed the survey through Autism Action please post the forms back to the investigators in the envelope provided.

Thank-you for taking the time to participate in this survey.

5.6. Appendix 6: Consent Form

Prevalence and Patterns of Medication Use in Children and Adolescents with Autism Spectrum Disorders in the Western Cape Consent Form

I,_____ (full name), the parent/ guardian of _____(full name) give consent for the information I have given in the questionnaire and Nisonger Child Behaviour Rating Form to be used in the study on the prevalence and patterns of medication use in children and adolescents with autistic spectrum disorders in the Western Cape.

I have read and understood the information sheet of this survey. I understand that my participation in this study is entirely voluntary and should I choose not to participate, I will not be prejudiced in any way. I understand that full confidentiality will be maintained at all times and that consent can be withdrawn at any time.

Signed:_____

Date (Day, Month, Year:)_____

Place:_____

This study has been reviewed and approved by the University of Cape Town Research Ethics Committee. If you have any questions about this study contact:

Professor Marc Blockman (Head of Faculty of Health Sciences Research Ethics Committee)

Tel: 021 406 6338

e-mail: marc.blockman@uct.uct.ac.za

Dr Kerry-Ann Louw (Investigator)

Tel : 021 685 4103

e-mail : medicationsurvey@gmail.com

5.7. Appendix 7: Assent Form

Prevalence and Patterns of Medication Use in Children and Adolescents with Autism Spectrum Disorders in the Western Cape Assent Form for Children Aged 18 years

I,_____ (full name), give assent for the information given in the questionnaire and Nisonger Child Behaviour Rating Form to be used in the study on the prevalence and patterns of medication use in children and adolescents with autistic spectrum disorders in the Western Cape.

I have read and understood the information sheet of this survey. I understand that my participation in this study is entirely voluntary and should I choose not to participate, I will not be prejudiced in any way. I understand that full confidentiality will be maintained at all times and that consent can be withdrawn at any time.

Signed:_____

Date (Day, Month, Year:)_____

Place:_____

This study has been reviewed and approved by the University of Cape Town Research Ethics Committee. If you have any questions about this study contact:

Professor Marc Blockman (Head of Faculty of Health Sciences Research Ethics Committee)

Tel: 021 406 6338

e-mail: marc.blockman@uct.uct.ac.za

Dr Kerry-Ann Louw (Investigator)

Tel : 021 685 4103

e-mail : medicationsurvey@gmail.com

Part B:Literature Review

1. Objectives of the Literature Review

A structured search was conducted to review the current literature on the prevalence of medication use amongst individuals with autism spectrum disorders (ASD), evidence for the use of psychotropic medication in individuals with ASD and evidence for the use of over the counter preparations, special diets, complementary and alternative medicines in individuals with ASD.

2. Literature Search Strategy

A search was conducted in PubMed using the following key terms: “autism”, “autism spectrum disorders”, “treatment”, “medication”, “complementary and alternative medicines”. The search was confined to literature in English. Human studies including children and adults were included. All time periods were searched. The earliest relevant paper identified was published in 1988. Studies were also identified using the reference lists of the papers generated from the original search.

3. Summary of Literature

3.1 Introduction

The pervasive developmental disorders (PDD) are a group of neurobiological conditions, evident in the first few years of life, that follow a chronic course and are characterised by pervasive dysfunction in three core domains: reciprocal social interaction, communication and stereotyped behaviours (American Psychiatric Association, 2000). The DSM-IV (American Psychiatric Association, 2000) defines five PDD: Autistic Disorder, Rett’s Disorder, Childhood Disintegrative Disorder, Asperger’s Disorder and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). The Autism Spectrum Disorders (ASD) include Autistic Disorder, Asperger’s Disorder and PDD-NOS. These

conditions show marked clinical heterogeneity with changing symptomatology relating to developmental stage (Seltzer, et al., 2003).

The prevalence rates of Autistic Disorder vary markedly between epidemiological studies. According to the DSM IV, the mean prevalence rate is 5 cases per 10 000 with a range of 2 to 20 cases per 10 000 individuals (American Psychiatric Association, 2000). Although evidence is lacking, PDD-NOS and Asperger's Disorder appear to be more common (Bernet, et al., 1999). More recent United States of American estimates predict that 3 to 6 out of every 1000 children will have autism (National Institute of Health, 2009). These figures were concordant with data from studies from multiple sites and using varying methodologies (Geschwind, 2009). A 2009 review stated prevalence rates for ASD between 1 per 150 and 1 per 200 individuals and rates of 1 per 500 for the diagnosis of strictly defined autism (Geschwind, 2009). The apparent rise in prevalence remains a controversial issue and may be related to improved identification, and not a true rise, in incidence (Gurney, et al., 2003). According to the statistics of Autism Western Cape, 1 in 86 South African children under the age of 6 is affected by autism and 10 children per week are being diagnosed at the Red Cross, Tygerberg and Lentegeur Psychiatric Hospitals (Autism Western Cape, 2009). These statistics have not been scientifically validated and may be an over estimate

There is no cure for autism, but behavioural and pharmacological interventions are aimed at reducing core symptoms, managing other problem behaviours and treating psychiatric comorbidities. This allows for improved level of functioning and quality of life (Deokar, et al., 2008). Dysfunctional behaviours interfere with educational and rehabilitation interventions and can cause significant distress (Bernet, et al., 1999). Early identification of ASD and the implementation of sustained, appropriate educational and behavioural interventions improves long term clinical outcomes (Bernet, et al., 1999) (Tsai, 1999).

Despite the implementation of educational and behavioural interventions, many individuals remain impaired and distressed and the use of pharmacological interventions becomes necessary (Posey, et

al., 2001). To date, risperidone is the only medication approved by the U.S Food and Drug Administration (FDA)for the treatment of problem behaviours, specifically irritability, aggression and self-injury, in children with autism (Food and Drug Administration, 2006). Psychotropic medications from all classes are currently in use including antidepressants, mood stabilizers, antipsychotics, antihypertensives and stimulants. Alternative and more easily obtainable over the counter (OTC) treatments such as megadose vitamins, herbal remedies and specialized diets are also used. There is minimal data about the long term safety of any of these agents (McCracken, 2005).

3.2 Prevalence of medication use in ASD

Medication surveys in the field of intellectual disability exposed elevated prescribing rates and served to guide changes in prescribing practices in the United States of America (Aman, et al., 2003). These studies did not specifically address ASD.

There have been several scientific prevalence studies since 1995 which show that the ASD population is highly medicated, and is becoming increasingly medicated (Aman, et al., 1995) (Martin, et al., 1999) (Langworthy-Lam, et al., 2002) (Aman, et al., 2003) (Witwer, et al., 2005) (Aman, et al., 2005) (Oswald, et al., 2007) (Gurney, et al., 2006) (Mandell, et al., 2008) (Esbensen, et al., 2009) (Rosenberg, et al., 2010). This body of epidemiological data is growing in parallel with systematic reviews into evidence supporting prescribing practices in ASD. These reviews reveal an urgent need for placebo-controlled trials of commonly prescribed medications (Tsai, 1999) (Posey, et al., 2001) (King, 2000) (Bodfish, 2004) (Palermo, et al., 2004) (Kwok, 2003) (Findling, 2005) (Leskovec, et al., 2008) (Mc Dougle, et al., 2008) (Parikh, et al., 2008) (Siegel, et al., 2011) (McPheetters, et al., 2011) (Huffman, et al., 2011) (Warren, et al., 2011). The number of randomized controlled trials targeting the ASD population has increased over the last decade (Siegel, et al., 2011).

Most available data on the prevalence of medication use in ASD comes from the United States of America. The first medication prevalence survey was conducted by Rimland in 1988 (Rimland, 1988).

This was an informal survey completed by approximately 4000 parents of autistic children. The questionnaire included parental efficacy ratings. Thioridazine was the most commonly used drug (n=724), but high dose vitamin B6 and magnesium received the highest ratings for behavioural improvement.

The first scientific study was a point prevalence survey conducted in the Autism Society of North Carolina in 1992 and 1993 (Aman, et al., 1995). The questionnaire elicited demographic and medication use information, specific data related to epilepsy, as well as parent satisfaction with treatment. Of the 838 respondents aged 1 to 82, 33.8% of the sample were taking some psychotropic drug or vitamin for autism or associated behavioural or psychiatric problems. If all agents, including vitamins, antiepileptics and other physical treatments were included, over 50% of the population were medicated. Neuroleptics were the most prevalent group (12.2%) with greater use of thioridazine than haloperidol. The next most commonly used drugs in order were: psychostimulants (6.6%), anxiolytics (6.3%), antidepresants (6.1%), antihypertensives (4.4%) and mood stabilizers (3.9%). Antiepileptic medications were considered as mood stabilizers in the absence of comorbid epilepsy. Of the sample, 19.2% were taking vitamins and 13.2% anticonvulsants. Age and type of housing (a proxy variable reflecting difficulty in management) were found to be independent predictors of psychotropic medication use.

A further two large point prevalence studies of medication use in individuals with ASD have since been conducted in questionnaire form (Aman, et al., 2003) (Langworthy-Lam, et al., 2002). The second study was done in the Autism Society of Ohio in 1999 and the third in the Autism Society of Carolina in 2001 (NC2). The three studies were done by the same group utilizing the same questionnaire and were later compared to assess longitudinal trends and regional effects (Aman, et al., 2005). There were significant increases in medication use with time.

In the second Northern Carolina study, of the 1538 respondents between the ages 3 and 56, 45.7% of individuals with autism were taking psychotropic drugs (Langworthy-Lam, et al., 2002). This

increased to 53.1% with the inclusion of vitamins and antiepileptics. Antidepressants were the most commonly used psychotropic medication (21.7% of the sample), followed by antipsychotics (16.8%) and stimulants (13.9%). The longitudinal trend was a very large increase in antidepressant utilization with significant increases also occuring in antipsychotic, psychostimulant and anitihypertensive utilization. Changing patterns were thought to reflect increased physician prescribing of the newer selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics. The first Carolina study had been completed before the introduction of these agents. These medications have greater perceived safety as well as a growing body of evidence to support their use (Mc Dougle, et al., 2008) (Leskovec, et al., 2008). In keeping with previous findings, greater age and greater severity of autism and intellectual disablility predicted psychotropic medication use. Interestingly, younger autistic individuals had increased use of autism supplements; possibly because parents of younger indivduals seek out more "natural" remedies.

The Ohio study survey included 417 respondents aged 2 to 46 and findings were consistent with the second Northern Carolina study (Aman, et al., 2003). This went against the authors' original hypothesis that there would be less medication use in Northern Carolina because of greater access to psychoeducational services.There was significantly greater use of supplements for autism in the Ohio group. There were strong demographic variable correlates between all three studies, with greater age and level of disability and more restrictive placement being associated with increased medication use.

Psychotropic medication has been investigated in a specific subgroup of individuals with higher functioning autism and Asperger's disorder (Martin, et al., 1999). In addition to demographic and medication information, data collection included developmental, behavioural and educational inventories such as the Autism Behaviour Checklist (ABC). The sample was drawn from children, adolescents and adults attending the Yale Child Study Center's Project on Social Learning Disabilites and was therefore not a naturalistic sample. Of 109 children, adolescents and adults, 55% were

taking psychotropic medications with 29.3% taking more than one medication. These findings reflect similar rates to those of the general ASD population. Antidepressants were the most commonly used agents (32.1%) followed by stimulants (20.2%) and antipsychotics (16.5%). The high rate of SSRI use was again attributed to presciption practices related to limited side effect profile and the perception of the "benign" nature of these medications. An added dimension to this study was the inclusion of prescribing practices. Medications had been prescribed by general psychiatrists in 58.3% of the sample, child psychiatrists in 26.7% and by neurologists and paediatricians in 10%. There was marked clinical heterogeneity within the sample, with many symptoms that were unrelated to the core features of autism being treated pharmacologically. Of note were the high rates of depression and anxiety symptoms.

The above studies are all point prevalence studies which are reliable in extracting information about current medication use, but limited in reflecting the use of medications that are not constantly administered. This aspect was addressed in a study by Witwer and Lecavelier where information was obtained from 353 participants regarding 1 year rates and patterns of medication use (Witwer, et al., 2005). The aim of the study was to focus on the younger population with the inclusion criterion of age between 3 and 21 years. Parents also completed the Nisonger Child Behaviour Rating Form to identify problem behaviours and the Scale of Independent Behaviour-Revised, which is a standardized measure of adaptive behaviour. The one year rates of medication use were found to be similar to previous point-prevalence studies, supporting the reliability of point prevalence data. Of the subjects, 46.7% had taken at least one psychotropic medication in 1 year, 17.3% some type of vitamin and 15.5% were on a specialized diet. The most prevalent medications were psychostimulants (24%), followed by antidepressants (21.2%), antipsychotics (19.5%), alpha agonists (10.9%) and mood stabilizers (4.2%). Compared to previous studies, a higher percentage of children and adolescents were taking psychostimulants and antipsychotics. Differences in neuroleptics were accounted for by the increasing trend of atypical antipsychotic prescribing, due to mounting supportive evidence. Methodological differences between the studies were also thought to

contribute to the higher percentage of respondents having used antipsychotics, as children may have been given brief trials of antipsychotics over the year. Stimulant use was thought to be higher because of the nature of the age demographic of the sample. Greater age, lower adaptive skills and social competence and higher levels of problem behaviour were associated with greater medication use.

The findings of these large questionnaire based surveys are supported by evidence from cross-sectional telephone (Gurney, et al., 2006) and internet surveys (The Interactive Autism Network, 2008) (Green, et al., 2006).

A limitation of surveys that utilise parental reporting is that they rely on parent recollections. Several studies have addressed this issue by altering methodological design to draw on information from various sources of medical records and databases (Oswald, et al., 2007) (Mandell, et al., 2008) (Shimabukuro, et al., 2008) (Rosenberg, et al., 2010). With access to large databases and without the limitation of non-response, sample sizes tend to be much larger. The findings from these studies are discussed below.

Oswald and others collected data from the 2002 commercial claims and encounters databases of a healthcare information company (Oswald, et al., 2007). Their sample included all individuals under the age of 21 and information was reviewed regarding demographics, medication use as well as inpatient admissions and outpatient visits. Of the 2390 individuals with ASD, 83% had at least one drug claim in the last year from 125 medication classes. Of the sample, 57% received psychotropic or anticonvulsant medications. This finding is in keeping with point prevalence studies and supports the reliablility of the parent survey data. The most common class of psychotropic medication used was antidepressants (32.1%) followed by stimulants (26.9%), antipsychotics (23.5%), anticonvulsants (15.2%), hypotensive agents (11.9%), hypnotics (5.8%) and benzodiazepines (4.2%). Antidepressants, antipsychotics and anticonvulsants showed increasing use with age. A limitation was that this study did not include over the counter drugs. Another concern, despite this being a commonly used

methodology, is that data reflects what prescriptions were filled, and not whether medications were actually taken.

Mandell and others conducted a cross-sectional study of 60641 children with ASD using Medicaid claims from 2001 to determine patterns of psychotropic medication use (Mandell, et al., 2008). Medicaid is the United States Health care programme for individuals with low incomes and resources and it includes individuals with disabilities (Wikipedia, 2009). The study collected demographic data, information regarding psychotropic medication use and data on County and State characteristics. Of the sample, 56% used at least 1 psychotropic medication during 2001, with 20% of these using more than 3 concurrently. Neuroleptics were the most common (31%), followed by antidepressants (25%), stimulants (22%), mood stabilizers (21%), anxiolytics (12%) and sedatives (3%). Older children were more likely to use medication. Children in foster care had the highest rates of use of psychotropic medications. Children who had an inpatient stay were more likely to use medication. Differences were found between the ASD, with 61% of children with Asperger's disorder and PDD-NOS taking psychotropic medications and 53% of children with an Autistic disorder diagnosis taking psychotropic medications.The proportions of individuals using medications in this study could be higher than community based samples, because children accessing Medicaid may be more severely affected by autism.

Rosenberg and others examined psychotropic medication use among 5 181 children aged 18 years and younger with ASD enrolled in a national web-based registry (Rosenberg, et al., 2010). The Interactive Autism Network is an internet based research database that continually collects data from families of children with ASD. Of the total sample, 35% were using at least one psychotropic medication. The most commonly reported psychotropics were stimulants (15.4%), neuroleptics (15%) and antidepressants (13.6%). Patients insured by Medicaid were more likely to use medications. The majority of psychotropics were prescribed by psychiatrists or neurologists.

Psychotropic use was more likely in children of older age, children with intellectual disability or psychiatric comorbidity.

A study by Shimabukuro and others analysed medical expenditures data collected from a large USA market research databases (Shimabukuro, et al., 2008). On average, medical expenditures for children and adolescents with ASD were 4.1 to 6.2 times greater than for those without ASD. In keeping with the above studies psychoactive medication use was positively associated with increasing age.

To date, there has been only one longitudinal study of medication use among individuals with ASD (Esbensen, et al., 2009). Esbensen and others examined 286 adolescents (10 years or older) and adults over a 4.5 year period. Their findings confirmed the high prevalence rates of medication use and the increasing use of medication over time. Initially 70% of individuals were taking psychotropic or non psychotropic medications. This increased to 81%, 4.5 years later. At the beginning of the study, 57% took at least one psychotropic medication and 37% took at least one non-psychotropic medication. For both types of medication, the number of medications and the proportion of individuals taking medications increased with time. Of the nonmedicated individuals in the sample, 30% began taking medication during the study timeframe. Higher rates of medication use than those presented in previous studies can be related to the older age of the sample. Older age has already been shown to predict increasing medication use (Aman, et al., 2005). Adolescents have an increased risk of developing seizure disorder and psychiatric comorbidity (American Psychiatric Association, 2000) which could explain greater medication use with age. The longitudinal increases in medication use could reflect changes in prescribing practices as discussed above. The authors conclude that more people with ASD are taking medications and that more medications are taken over time. Individuals who are medicated are likely to stay this way, the pattern being more pronounced for psychotropic medications.

The above studies use various methodologies to explore the prevalence and patterns of psychotropic use among idviduals with ASD. Despite the various methodologies, all studies report similar findings. Findings from the longitudinal study and studies using large databases show similar data to those of point prevalence survey studies. This population is highly medicated with increasing use of medications reflecting changes in prescibing patterns.

The following table summarises the frequency of use of specific drugs reported in the studies above.

Table summarising the frequency of use of specific drugs reported in the studies discussed above.

Study	Percentage of the Sample Taking Medication						
	Psychotropics	**Anti-psychotics**	**Stimulants**	**Anxiolytics Hypnotics**	**Anti-depressants**	**Anti-hypertensives**	**Mood Stabilisers**
Aman et al 1995 Point prevalence survey	33.8	12.2	6.6	6.3	6.1	4.4	3.9
Aman et al 2003 Point prevalence survey	45.6	14.9	11.3	8.7	21.6	12.5	4.5
Langworthy-Lam et al 2002 Point prevalence survey	45.7	16.8	13.9	7.3	21.7	9.5	5.1
Martin e al 1999 Point prevalence survey	55	16.5	20.2	6.4	32.1	6.4	9.2
Witwer and Lecavalier 1 year rates Survey	46.7	19.5	24	2.8	21.2	Reported individually	4.2
Oswald et al 2007 1 year rates Database	57	23.5	26.9	5.8	32.1	11.9	Not classified separate from anti-convulsants
Mandell et al 2008 1 year rates Database	56	31	22	12	25	Not reported	21
Rosenberg et al Point prevalence Database	35.3	15	15.4	<2	13.6	Not reported	6.6
Esbensen et al 2009 Longitudinal Time 1	57	24	12	10	33	Not reported	Not classified separate from anti-convulsants
Esbensen et al 2009 Longitudinal Time 4	64	33	7	14	43	Not reported	Not classified separate from anti-convulsants

There have also been studies that have focused exclusively on the prevalence of use of complementary and alternative medicines in the ASD population. The definition of complementary and alternative medical therapy differs in different texts and can include a variety of therapies such as food supplements, modified diet, herbal remedies, vitamins and minerals, over the counter medications, as well as mind-body techniques such as meditation and accupuncture. United States of American national estimates report that approximately 2% of all children use complementary and alternative medicines (Davis, et al., 2003). These estimates are higher for children with disability or chronic illness (Hanson, et al., 2007). There is a vast amount of literature promoting these therapies in ASD, however there have been few published studies that focus on the supporting evidence base and the prevalence of these therapies. The findings from two recent prevalence studies will be discussed below.

A 2006 study by Hansen and others found that 74% of 112 families surveyed used complementary or alternative medicines for their child with ASD (Hanson, et al., 2007). This group defined complementary and alternative medicines as modified diet, food supplements, herbal remedies, vitamins, minerals, biofeedback, chiropractic and osteopathic manipulation, guided imagery, healer touching, massage, meditation, prayer and special exercises. Biologically based therapies were used in 54% of the sample and these included modified diet (38%), vitamins/minerals (30%), food supplements (23%), herbal remedies (11%) and secretin (8%). Several reasons for parents seeking out alternative therapies are listed in the discussion and included the lack of a single treatment for the core symptoms for autism, poor access to treatment, the perception that such treatments are more “natural”and concerns around the dangers of prescription medications.

A 2007 study by Wong and Smith compared the use of complementary and alternative medical therapies in a group of children with ASD (n=50) with a control group (n=50) (Wong, et al., 2006). Parents were asked about alternative medical systems (aromatherapy, homeopathic remedies, acupuncture, naturopathic remedies), biological based therapies (diets, mineral supplements,

mineral and vitamin supplements, vitamin supplements), manipulative and body based therapies (body based relaxation therapies, chiropractic, massage, sensory integration, therapeutic horseback riding) and mind-body and psychological therapies (music therapy, spiritual healing). More than half of the parents in the ASD group reported using or had used at least one of these therapies for their child (52%) compared to only 28% of the control group. The majority had used one or two therapies.

To our knowledge, there is no published evidence regarding the prevalence and pattern of psychotropic or over the counter medication use in children with ASD within the South African or African context.

3.3 Psychotropic medications in ASD

Despite the growing prevelance of medication use in this population, the evidence base to support the prescribing of medications remains small. The pathogenesis of autism is not fully understood and as yet there is no cure (Kwok, 2003). First line interventions include behavioural and cognitive strategies. These include parental counselling, behaviour modification, special education techniques, sensory integration training, speech therapy, social skills training and other communication and social interventions (Tsai, 1999) (Bodfish, 2004). Applied behaviour analysis (ABA) has a large body of supportive evidence (Geschwind, 2009). These interventions are thought to be most powerful when initiated early on. A recent systematic review of interventions for children ages 2 to 12 wth ASD was conducted by the Vanderbilt Evidence-based Practice Center (Warren, et al., 2011). The reviewers found that evidence supported early intensive behavioural and developmental interventions. However, lack of consistent data limited understanding of whether these interventions were linked to clinically meaningful changes in functioning.

Distressing and abberant behaviours interfere with the implementation of behavioural and educational interventions. Medication targets these distressing and abberant behaviours. This enhances the individual's ability to participate in these programmes and improves the positive

response to behavioural and cognitive strategies (Tsai, 1999) (Kwok, 2003). Effective pharmacological treatments are needed to assist children to achieve their full potential in the least restrictive environment (Siegel, et al., 2011).

While the core features of autism include impairments in social interactions, impaired communication skills and stereotyped patterns of behaviour, interests and activities; other behaviour symptoms are common. According to Tsai, about 60% have poor attention and concentration; 40% are hyperactive; 43%-88% exhibit morbid or unusual preoccupation; 37% have obsessive phenomena; 16%-85% show compulsions or rituals; 50%-89% demontrate stereotyped utterances; 70% exhibit stereotyped mannerisms; 17%-74% have anxiety or fears; 9%-44% show depressive mood, irritability, agitation and inappropriate affect; 11% have sleep problems; 24 %-43 % have a history of self injury; and 8% have tics (Tsai, 1999). These behaviours, which were previously thought to be associated features of autism, are now considered to be features of coexisting neuropsychiatric conditions such as attention deficit hyperactivity disorder (ADHD), affective disorders, obsessive compulsive disorder and Tourette disorder (Tsai, 1999). These associated behavioural symptoms may be amenable to medical therapy.

Psychiatric comorbidities are common in children with ASD with estimate prevalence rates between 25%-70% (Geschwind, 2009). A population derived cohort study found high rates of psychiatric disorders and frequently multiple disorders in children with ASD (Simonoff, et al., 2008). Of the 112 participants, 70% had one disorder and 41% had 2 or more disorders. The most common diagnosis was social anxiety disorder (29,2%), followed by ADHD (28,2%) and oppositional defiant disorder (28,1%). Clinical dysfunctions in other domains are also common in individuals with ASD. These include sensory abnormalities, developmental regression, motor signs such as hypotonia and apraxia, gross motor delay, sleep disturbance, and gastrointestinal disturbance (Geschwind, 2009). Comorbid medical disorders are found in 10%-15% of individuals with autism (Steyn, et al., 2003).

Studies show that neurochemical factors play a role in the pathogenesis of autism. These theories provide the rationale for psychopharmacological practices. Tsai summarized neurochemical data in his 1999 review. Theories exploring the role of serotonin in autism include those of hyperserotonemia, decreased serotonin binding and decreased central serotonergic responsivity. Current evidence concerning the role of dopamine in autism is mixed, but dopamine agonists have been shown to worsen preexisting stereotypies, aggression and hyperactivity. The evidence regarding norepinephrine and epinephrine is also inconclusive with some studies showing lower levels in individuals with autism. Neuropeptide studies have shown abnormalities in autistic subjects and autistic behaviours resembling opiate-induced behaviours in animals and certain behaviours seen in adult oppiate addicts (Tsai, 1999). In a recent review, Parikh and others discussed the neurochemical underpinnings of aggressive and self injurious behaviours in individuals with autism (Parikh, et al., 2008). Several studies related to the dopaminergic and serotonergic systems as well as the noradrenergic and endogenous opioid systems are cited (Parikh, et al., 2008).

There have been a number of reviews in the past decade concerning the evidence base supporting prescribing practices in individuals with autism. Medication studies differ widely in terms of study sample, sample size, research design, purpose of treatments and measures of response (Huffman, et al., 2011). There are several medications that have been identified as possibly being effective in treating autism, but additional clinical trials are much needed (Leskovec, et al., 2008). There have been four recent systematic reviews of medications used in children with ASD. These reviews used different study inclusion criteria, assessed different targets of treatment and used different methods of assessing the strength of the included studies. The findings of these three reviews will be discussed below.

The 2011 review by McPheeters and others reviewed the evidence for antipsychotics, serotonin-reuptake inhibitor and stimulant medications used for children younger than twelve with ASD (McPheetters, et al., 2011). Studies were included based on criteria developed in consultation with

experts involved in ASD care. Studies had to include at least 30 participants and have been published after the year 2000. Two investigators independently assessed the studies using a quality assessment form developed by the review team and experts in the field. The reviewers identified 18 studies of medical interventions of which 10 were randomised controlled trials. The findings of this review are summarised as follows:

Antipsychotics: There were 4 RCTs of risperidone identified, two of which targetted challenging behaviour as the primary outcome (McCracken, et al., 2002) (Shea, et al., 2004). The studies showed a moderate improvement in challenging and repetitive behaviours. All RCT studies and prospective case series reported significant adverse events especially weight gain, sedation and extra pyramidal effects. Two 8-week, industry funded RCTs of aripiprazole showed improvement in challenging and repetitive behaviours (Owen, et al., 2009) (Marcus, et al., 2009). The most commonly reported adverse events were weight gain, sedation and extra-pyramidal effects.

Serotonin-Reuptake Inhibitors (SRI): A 12-week RCT of citalopram showed no significant difference betweeen groups (King, et al., 2009). Adverse events reported included activation symptoms and gastrointestinal effects. In a single cross over design RCT of fluoxetine versus placebo, subjects in the fluoxetine group showed greater changes in repetitive behaviours (Hollander, et al., 2005). The reviewers found the overall strength of evidence for the ability of serotonin reuptake inhibitor medications to reduce repetitive or challenging behaviours to be insufficient.

Psychostimulants: In a large, double blind placebo control study by the Research Units on Paediatric Psychopharmacology (RUPP) methylphenidate was shown to have efficacy but with reduced effectiveness and a less satisfactory side effect profile (Research Units on Pediatric Psychopharmacology Autism Network, 2005). Adverse effects reported included appetite and sleep changes, anxiety, depression, headache and diarrhoea. The reviewers found the strength of evidence for methylphenidate in reducing hyperactivity and challenging behaviour to be insufficient.

The reviewers conclude that most of the medications currently being used to treat children with ASD lack sufficient evidence. Risperdone and aripiprazole were found to be the two best studied medications for ASDs. Both challenging and repetitive behaviours showed improvement in these trials. However their significant association with adverse effects limits their use.

The 2011 systematic review of psychotropic medications in children with ASD by Siegel and Beaulieu included all typically prescribed psychotropic agents having undergone randomised controlled trial in participants 18 years old or younger (Siegel, et al., 2011). There was no date of publication exclusion criterion. The review was conducted using methodology developed by Reichow and colleagues to evaluate the quality of research in autism. The *Evaluative Method for Determining Evidence Based Practice in Autism* uses quality indicators to determine the strength of a study then assigning an evidence rating by combining the amount and quality of studies performed on an intervention (Reichow, et al., 2008). Thirty-three RCTs were included in the review. The results of the review are summarised below:

Alpha-2 Agonists: Clonidine and guanfacine both had insuficient evidence to recommend their use.

Antipsychotics: In keeping with the McPheeters et al review, riperidone was found to have established evidence for efficacy in the treatment of irritability and hyperactivity, and preliminary evidence for effficacy in reducing repetitive behaviours and stereotypy. The two industry funded trials of aripiprazole were found to have evidence for efficacy in reducing irritability, hyperactivity and stereotypy (Marcus, et al., 2009) (Owen, et al., 2009). Two older RCTs on haloperidol were reviewed (Anderson, et al., 1984) (Anderson, et al., 1989). Both studies received strong research ratings suggesting that there may be a role for haloperidol in cases of refractory negative behaviours. Risperidone was found to be superior to haloperidol in a head-to-head comparison (Miral, et al., 2008). However this study only obtained adequate research strength rating. Due to a weak research strength rating and the high frequency of weight gain, olanzapine was not recommended as a first-line agent.

Mood stabilisers: The evidence for divalproex sodium was mixed and found to be insufficient for use to treat irritability in children with ASD. Lamotrigine and levitiracetam had been studied in one RCT each with no evidence of an effect when compared to placebo (Belsito, et al., 2001) (Wasserman, et al., 2006).

Norepinephrine reuptake inhibitors: Based on a small RCT there was preliminary evidence for the efficacy of atomoxetine for hyperactivity (Arnold, et al., 2006).

Serotonin reuptake inhibitors: The citalopram RCT by King and others obtained a strong research rating but found no significant effects on repetitive behaviour (King, et al., 2009). The fluoxetine cross over RCT by Hollander and others obtained a weak research strength rating with positive but likely insignificant results (Hollander, et al., 2005). There was insufficient evidence to support the use of clomipramine.

Stimulants: The reviewers identified three RCTs, including the RUPP study, investigating methylphenidate (Research Units on Pediatric Psychopharmacology Autism Network, 2005) (Handen, et al., 2000) (Quintana, et al., 1995). Overall the level of evidence for methylphenidate in the treatment of hyperactivity in children with ASD was promising.

Miscellaneous agents: The reviewers found that there was insufficient evidence for amantadine, cyproheptadine and donepezil. Naltroxone studies had conflicting results. There was preliminary evidence for the use of pentoxifylline, a methylxanthine with immunologic and serotonergic effects, for the treatment of irritability and social withdrawal.

The reviewers concluded that only a few psychotropic medication had strong enough research data to obtain a rating of " Established Evidence". Risperidone and aripirazole had established evidence for treatment of irritability and hyperactivity and aripiprazole also had established evidence for the treatment of stereotypy. Haloperidol had established evidence for the treatment of negative behaviours. Medications with preliminary evidence included methylphenidate, naltrexone and

atomoxetine for the treatment of hyperactivity; riperidone for repetitive behaviour and stereotypy and pentoxyfilline in combination with riperidone for irritability and social withdrawal. The reviewers identified several limitations of pharmacotherapy trials in the ASD population including heterogeneity in the autism phenotype and the lack of accepted diagnostic tools to establish co-ocurring psychopathology.

The 2011 review of pharmacological treatments for ASD by Huffman and others included studies from 1994 to 2007 of individuals 0-22 years of age (Huffman, et al., 2011). There were 89 articles addressing pharamcological treatments identified. Reviewers used methodology in keeping with the Cochrane Collaboration for their literature review. Study quality assessment was based on domains used in the National Standards Project of the National Autism Center. Studies were allocated a score based on a Scientific Merit Rating Scale. This review included studies of complementary-alternative medicine (CAM) treatments which will be discussed below. Treatment response was organised by ASD symptoms, differentiating core and associated symptoms. Core symptoms were categorized as general; impaired social interaction; impaired communication and restricted, repetitive behaviour. Associated symptoms included maladaptive behaviour symptoms; which were further categorized into general, hyperactivity and aggression; and dysregulation symptoms which were divided into irritability, sleep problems, sensory abnormalities and gastrointestinal problems. **Risperidone** was found to be efficacious and safe for core symptoms, maladaptive behaviour, hyperactivity and irritability. **Methylphenidate** was effective in reducing symptoms of inattention and hyperactivity. All other medications included in this review were found to have marginal evidence only or to be ineffective. The reviewers concluded that many pharmacological treatments have minimal or no emperical data to support their use. Medications may show benefit in certain target areas but not others.

The Vanderbilt Evidence-based Practice Center systematically reviewed studies on therapies for children ages 2 to 12 with ASD published in English from January 2000 to May 2010 (Warren, et al.,

2011). This review included medications, complementary and alternative medicines (discussed below) and behavioural interventions. Study inclusion and exclusion criteria were developed in consultation with a technical expert panel. The authors used methods outlined by the Evidence-based Pracice Center to assess the quality of individual studies. Of 159 studies included 13 were found to be good quality, 56 were fair and 90 were poor. A total of 42 medication studies were identified of which 27 were RCTs. The authors concluded that the antipsychotic drugs **risperidone** and **aripiprazole** are the best studied medications in ASD and that they demonstrated significant improvement in challenging behaviour. These behaviours included emotional distress, aggression, hyperactivity, and self injury. The authors note however that medication side effects are significant. Both risperidone and aripiprazole caused weight gain, sedation and extrapyramidal symptoms. The strength of evidence for SRIs and stimulants was found to be insufficient. No medical treatments demonstrated benefit for social or communication symptoms in ASD.

3.4 Over the counter preparations, special diets, complementary and alternative medicines in ASD

A range of special diets, dietary supplements, vitamins, minerals and complementary and alternative medicines have been used in ASD. These have very limited supporting data. The review by the Vanderbilt Evidence-based Practice Center found that there was insufficient evidence to assess supplements and other agents including omega 3 fatty acids (Warren, et al., 2011). The 2011 review by Huffman and others identified 26 articles addressing complementary and alternative medicines (Huffman, et al., 2011). There were inadequate number of studies to draw conclusions about the benefit of these agents in treating core or associated symptoms of ASD. A 2010 review of complementary and alternative medicines in autism identified several agents as being safe, but very few had evidence to support their efficacy (Atkins, et al., 2010). Melatonin was considered to be safe and effective in treating sleep difficulties. The following agents were identified as being safe but with unknown efficacy: vitamin C, mulivitamins, vitamin B6, magnesium, carnosine, carnitine, essential

fatty acids, methyl B12, folic acid, glutathione, dimethylglycine, gluten free diets, casein free diets. Secretin was considered safe but there was good evidence that it is not efficacious.

3.5 Conclusion

Autism spectrum disorders are a complex group of imprecisely described disorders with a wide range of clinical and behavioural manifestations. It is unlikely that any specific set of interventions would address all the clinical problems associated with these disorders. This adds to the difficulty in interpreting the literature which includes studies that may not be comparable.

The key findings of this literature review include:

- The autism spectrum disorder population is a highly medicated group.
- There is limited data to support the prescribing of psychotropic medications in this population.
- There is currently insufficient data to support the use of over the counter preparations, special diets or alternative and complementary medicines in this population.

3.6 Limitations of the literature

There is a vast literature around medication and OTC prescribing in the ASD population. However, there are marked inconsistencies when comparing the methodology between published studies. This makes it difficult to summarise and review the literature as a whole. Firstly, the definition and diagnosis of ASD conditions varies between studies. Authors use different diagnostic tools and it often unclear from the literature how diagnoses were made and how severity of autism has been determined. Studies also target different populations within the ASD community and again this brings into question comparisons made across studies. Some studies have looked at children only while other include all age groups. Secondly, medications are classed differently in studies. For example in some cases antiepileptics were seperated as mood stabilisers while in others they were grouped broadly as anticonvulsants. As another example antihypertensives were reported in some

studies as a single category while in others they were seperated according to their mechanism of action. The literature around over the counter and complementary medications is even more confusing with authors using different definitions and OTC classification systems. Thirdly, studies have used different methods of collecting data. There are large point prevalence surveys as well as large database studies. Survey information is limited by recall and reporting bias while database data may not reflect real life practice. There has only been one longitudinal study which is a large gap in this body of literature. Longitundinal studies provide valuable information reflecting changing prescribing practices as well as reflecting the changing symptomatology of these disorders as individuals age. Even though studies using different methologies have all shown that this group is highly medicated, the differing methodologies make comparisons difficult. There is a need for large, multicenter, coordinated research.

The recent publication of medication systematic reviews provides valuable information about the evidence base supporting prescribing practices in the ASD population. The overwhelming conclusion is that evidence supporting prescribing practices is lacking. This is particularly evident in the CAM and OTC literature. The medication systematic review literature is problematic. Each review used different inclusion criteria, assessed different targets of treatment and used different methods of assessing the strength of the evidence. This makes the literature hard to compare and confusing to interpret. These differences may reflect the lack of standardised diagnostic methods and treatment outcome measures in the ASD population. In general these disorders include a broad range of clinical and behavioural symptoms whose underlying neurobiology remains poorly understood. This may explain the inconsistencies found in the literature.

None of the studies explored the stigma surrounding medication use in this population or the reasons why parents or individuals choose to use certain medications. There are a many cultural factors that affect access to health care and adherance practices and this has not been addressed in these studies. This information would be valuable in informing prescribing practices.

The is limited research around ASD in the African and South African context. Differences in diagnosing and prescribing practices would make comparisons to international literature difficult.

4. Need for Further Research

To our knowledge, there is no evidence regarding the prevalence and pattern of medication use in children with ASD within the South African and African context. Our unique demographic and social environment may reflect patterns that are not in keeping with international trends. This knowledge is vital to inform clinical practice and guide future research. In the area of ASD particularly, there is persisting use of medications in the absence of an adequate evidence base. In a low resource setting such as South Africa evidence based guidelines are vital to inform prescribing practices.

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Part C: Results of Study in Manuscript Format

Prevalence and Patterns of Medication Use in Children and Adolescents with Autism Spectrum Disorders in the Western Cape

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Abstract

Objective: This study was conducted to investigate the prevalence and patterns of medication use amongst a sample of school going children and adolescents with autism spectrum disorders (ASD) in the Western Cape.

Method: This was a descriptive, quantitative, analytic study. A survey questionnaire and the Nisonger Child Behaviour Rating Form (NCBRF) were utilized to collect relevant data from parents of children and adolescents recruited from two schools for children with ASD in Cape Town. Participants were also recruited from the Autism Action database.

Results: A total of 24.6% of 65 children used psychotropic medications. Antipsychotics were the most commonly prescribed psychotropics followed by stimulants, antidepressants and mood stabilisers. Complementary and alternative medications were also commonly used with 40% of children using over the counter medications (OTC) and 15.4% being on a special diet for autism. Children of black or coloured ethnicity were less likely to use OTC medication than children in the white/asian ethnic group.

Conclusions: In keeping with international studies this sample of children with ASD was a highly medicated group. The findings of this pilot study were limited by the sample size but it provides valuable insight into medication use in the South African ASD population.

Background

The Autism Spectrum Disorders (ASD) are a group of neurobiological conditions characterised by pervasive dysfunction in three core domains: reciprocal interaction, communication and stereotyped behaviours (American Psychiatric Association 2000). The term ASD encompasses Autistic Disorder, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Prevalence rates of ASD vary between epidemiological studies. Approximately 6 out of every 1000 children have an ASD diagnosis (Johnson and Myers 2007). There is no cure for autism. The goal of treatment is to optimise the child's functioning by minimising core symptoms and treating other behavioural symptoms and psychiatric co-morbidities. There are several early, intensive behavioural and developmental interventions that demonstrate variable outcomes (Warren et al 2011a). Pharmacological treatments are aimed primarily at reducing distressing or disruptive behaviours to allow children to participate in cognitive and behavioural programmes (Kwok 2003). While reviews consistently conclude that there is a lack of evidence to support medication prescribing practices in the ASD population, prevalence studies show that this population remains highly medicated with both psychotropic and over the counter agents.

There have been several large population based prevalence studies that show that the ASD population is highly medicated (Aman et al 1995, Aman, Lam and Collier-Crespin 2003, Langworthy-Lam, Aman and Van Bourgondien 2002, Martin et al 1999, Witwer and Lecavalier 2005). These findings are supported by data from insurance claims and large database samples (Mandell et al 2008, Oswald and Sonenklar 2007, Rosenberg et al 2010). Medications include psychotropics and over the counter (OTC), complementary and alternative medicines. The most commonly prescribed psychotropic medications in the ASD population include antipsychotics, antidepressants and stimulants with 30-60% of children with ASD taking at least one psychotropic medication (Aman et al 1995, Langworthy-Lam et al 2002, Mandell et al 2008, Martin et al 1999, Oswald et al 2007, Rosenberg et al 2010). Older age, greater severity of autism and presence of disabilty or psychiatric

co-morbidity have been shown to predict psychotropic medication use (Aman et al 1995, Langworthy-Lam et al 2002, Mandell et al 2008, Oswald et al 2007, Rosenberg et al 2010).

There has been a growing number of randomised control trials of psychotropic medications in the ASD population in the last decade. However, the evidence base supporting current prescribing practices remains poor. Recent reviews concluded that most of the psychotropic medications used to treat children with ASD lack sufficient evidence (Huffman et al 2011, McPheeters et al 2011, Siegel and Beaulieu 2011, Warren et al 2011b). Risperidone has been the best studied psychotropic and it is currently the only medication approved by the Food and Drug Administration for the treatment of problem behaviours in children with autism. Notably, risperidone does not influence the core features of ASD, but rather the associated behaviours.

A range of special diets, dietary supplements, vitamins, minerals and other complementary or alternative medicines has been widely used in ASD (Akins, Angkustsiri and Hansen 2010, Hanson et al 2007, Warren et al 2011b, Wong and Smith 2006). These agents may be used to such a great extent because there is no cure for autism and because no pharmacologic agent has been shown to be effective in managing the core symptoms of autism (Hyman and Levy 2000). These agents are also perceived as being safer than prescribed medications (Hanson et al 2007).

The evidence for the efficacy of complementary and alternative medications in the ASD population also remains poor. The following agents have been identified as being safe but with unknown efficacy: vitamin C, mulivitamins, vitamin B6, magnesium, carnosine, carnitine, essential fatty acids, methyl B12, folic acid, glutathione, dimethylglycine, gluten free diets, casein free diets; and there is currently insufficient evidence to support their use (Akins et al 2010, Huffman et al 2011).

To our knowledge there is no published evidence regarding the prevalence and patterns of medication use in a South African (or African) ASD population and whether this mirrors the use of medications in children with ASD elsewhere. Knowledge of the use of medications in ASD in local

populations would assist in disseminating accurate information to professionals and families, which in turn would promote the development of rational and evidence based approaches to the management of children with ASD in South Africa.

Aims and objectives

The aim of this study was to investigate the prevalence and patterns of medication use amongst a sample of school going children and adolescents with ASD in the Western Cape. The first objective of the study was to describe the prevalence of the use of psychotropic medications, OTC preparations and special diets as well as to explore the patterns of prescribing including the designation of the prescriber and the indication for use. The second objective was to determine the relationship between sample variables (age, ethnicity, income and child behaviours) and medication use.

Methods

This was a descriptive, quantitative, analytic study.

Sample

The sample was purposefully ascertained and was drawn from two schools for children and adolescents with ASD and the database of Autism Action South Africa. Inclusion criteria included a formal ASD diagnosis, an age range between 3 and 18 years and that the child attend an educational service and reside in the Western Cape Province. Children with comorbid medical, psychiatric and neurodevelopmental conditions were not excluded from the study.

Alpha School for Autistic Children in Cape Town has over 60 learners between the ages of 4 and 18 years. Vera School for Autistic Children has approximately 100 learners. All children were diagnosed with ASD following an assessment by a multidisciplinary professional team which included a clinical psychologist. Children were diagnosed with ASD based on DSM-IV criteria and age appropriate rating scales including the Childhood Autism Rating Scale. Both schools serve children from the greater

Cape Town metropolitan area and to a lesser extent other regions within the Western Cape Province. Autism Action South Africa is an independent organisation with 300 registered members. Through Autism Action South Africa, parents of children who met inclusion criteria were invited to participate in the survey. Parents of learners attending Alpha and Vera Schools were issued with paper copies of the survey questionnaires for self-completion whilst survey participation requests were sent out via email to members of the Autism Action database.

Outcome measures

A survey questionnaire was adapted with permission from the author from that used in previous point prevalence studies of psychotropic medication use for ASD (Aman et al 1995). Data was collected on age, gender, ethnicity, total income, current medication use (including prescribed and OTC), special diet use, medication prescriber, indication for medication and presence of medical and psychiatric co-morbidity. For the purpose of this study OTC medications were defined as any non-prescription preparation taken by the child for any health promotion or treatment purposes. Questions about level of the child's intellectual disability and severity of autism were excluded from the questionnaire because of parental under reporting found in previous studies (Aman et al 1995).The questionnaire was developed in English and translated into Afrikaans where the latter was the parents' home language.

Participating parents completed the Nisonger Child Behaviour Rating Form (NCBRF) a standardized instrument for assessing behaviour in children and adolescents with intellectual and developmental disabilities. There are currently no child behaviour rating scales that have been adapted and validated in the South African population. The NCBRF has been validated in the United States and the subscales correspond highly with those of the Autism Behaviour Checklist (Aman et al 1996, Tasse et al 1996). It has been used in several international medication prevalence studies in the ASD population. The NCBRF has 10 social competence items. These are rated on a four-point Likert scale ranging from [0] not true to [3] completely or always true. Scoring is distributed on two subscales,

Compliant/Calm and Adaptive/ Social. The problem behaviour section consists of 66 items. These are rated on a Likert Scale from [0] if the behaviour did not occur or was not a problem to [3] if the behaviour occurred a lot or was a severe problem. The items are distributed on 6 subscales: Conduct Problem, Insecure/ Anxious, Hyperactive, Self-Injury/ Stereotypic, Self-Isolated/ Ritualistic and Overly Sensitive. The NCBRF has been translated into Afrikaans and it has been linguistically validated by the MAPI Institute (MAPI Institute 2009).

Data Analysis

Statistical analysis was conducted using SSPS Statictics 19. Anticonvulsants were grouped as mood stabilisers if epilepsy was not present. Point prevalence of medications was determined using frequency counts. Logistic regression analysis was used to determine whether there was any relationship between medication use and demographic (school, age, income, ethnicity) or behavioural measures (NCBRF subscales). For the analysis, income was grouped into two ranges, R0-R15999 and >R16000 per month, and R0-R15999 was used as the reference range. White and asian ethnicities were grouped together and used as the reference for the ethnic groupings.

Results

Response rates to the survey were 38% and 37% for Alpha School and Vera School respectively. There were 6 responses from the Autism Action data base. Of the 65 children, 35.4% attended Alpha School, 55.4% attended Vera School and 9.2% other schools. The demographic data of the children including a comparison between the schools is shown in *Table 1*. The majority of children (92.3%) were male, with a range of ethnicities and incomes. The median age of the children was 9 years (range 5-18 years). A total of 13.8% of children in this sample had been diagnosed with co-morbid psychiatric disorders, namely attention deficit hyperactivity disorder (ADHD) (9.2%), depression (1.5%), anxiety (1.5%), bipolar mood disorder (1.5%) and obsessive compulsive disorder (OCD) (1.5%). A substantial proportion of the children (40%) were also diagnosed with a medical condition,

the most commonly reported being allergic rhinitis (13.8%), asthma (13.8%), epilepsy (7.7%), sinusitis (4.6%), and eczema (3.1%). Of the total 24.6% of children were taking medications for a physical illness (*Table 2*).

A total of 24.6% of children took psychotropic medications. There was a difference in psychotropic medication use between the schools (see *Table 3*), with 27.8% of children from Vera School and 8.7% of children from Alpha School taking psychotropic medications. This difference was not statistically significant. Antiepileptics used for epilepsy were excluded from the psychotropic total, that is they were not rated as mood stabilisers. Antipsychotics (16.9%) were the most commonly prescribed psychotropics followed by stimulants (6.2%), antidepressants (6.2%) and mood stabilisers (3.1%). Risperidone was by far the most commonly reported prescribed psychotropic medication, being used by 15.4% of children.

Respondents reported that psychotropics were prescribed for a range of symptoms. The most common indication reported for any psychotropic medication used was problem behaviour (12.3%) followed by inattention and hyperactivity (10.8%), anxiety (4.6%), sleep difficulty (3.1%), mood stabilisation (3.1%), depression (1.5%) and psychotic symptoms (1.5%). In some cases several psychotropics were prescribed for a general symptom such as 'problem behaviour' while in other cases a specific drug had been prescribed for a specific indication such as inattention or depression. Of the antipsychotics, the most commonly prescribed in this sample, risperidone had been prescribed for a range of difficulties including problem behaviour, sleep difficulties, anxiety symptoms, attention problems and mood symptoms. One child was taking risperidone combined with quetiapine to target problem behaviour and ADHD. The other antipsychotic reportedly prescribed was sulpiride which had been prescribed to target psychotic symptoms. In all cases of reported methylphenidate use the indication for prescription was symptoms of inattention or ADHD. One child was taking atomoxetine in combination with methylphenidate for symptoms of inattention. Of the antidepressants fluoxetine was reportedly prescribed for depression in one child

and poor attention in another. Sertraline was prescribed for anxiety and imipramine for problem behaviours. Lithium and sodium valproate were prescribed to stabilise mood and target problem behaviours. Sodium valproate was also used as an anticonvulsant in three children with epilepsy. Lamotrigine and topiramate had been prescribed as anticonvulsants and not mood stabilisers.

Of the children taking any physical or psychotropic medication 29.6% reported current side effects on treatment. Many children were taking several medications in combination and respondents did not always identify which specific treatment was causing a side effect. Several respondents reported that they did not know whether their children were experiencing side effects on medication. The range of side effects reported included drooling (combination of epilim, topiramate, clobezam), vomiting (risperidone), sedation (risperidone), increased appetite (epilim), muscle spasms (risperidone), palpitations (methylphenidate) and emotional dysregulation (risperidone). Weight gain was reported as a side effect in five children. In three of the children weight gain was specifically attributed to a single drug namely risperidone, epilim and corticosteroids. For the other two children the combination of medications reported as responsible for weight gain were epilim, quetiapine and risperidone; and methylphenidate, atomoxetine and risperidone. Five of the ten children taking the most commonly prescribed psychotropic, risperidone, experienced side effects; although in two of these children it was taken in combination with other dugs and the respondents were unable to identify specifically which drug was responsible for the side effect. Side effects that were attributed specifically to risperidone were weight gain, sedation, muscle spasms, vomiting and emotional dysregulation. One child with comorbid diagnoses of OCD and bipolar mood disorder had previously been prescribed ziprasidone for behaviour problems but this had been stopped because of side effects of nausea, abdominal pain and sedation. At this time the child was found to have a fatty liver.

OTC medication and special diet use are summarised in *Table 4*. Of the total number of children 40% used OTC medications and 15.4% were on a specialist diet for autism. There were differences in OTC

use between the schools with 55.6% of children from Vera School and 13% of children from Alpha School taking OTC medications. This difference is not statistically significant. Of the total number of children, 16.9% were taking one OTC preparation, 13.8% two preparations and 9.2% three or more OTC preparations. A range of OTC medication was used including vitamins, minerals, dietary supplements, probiotics and homeopathic preparations. None of the children taking these preparations reported any side effects. Multivitamins (18.5%) and omega 3 and or 6 preparations (16.9%) were the most commonly taken preparations. A particular omega 3 and 6 brand, Eye Q, was used by 9.2% of the children. Gluten and casein free diets were the most commonly reported special diets. Three respondents reported that their children had tried special diets previously; including gluten, casein and sugar free diets; but that these had been stopped because no change in behaviour was seen.

The majority of medications and OTC preparations were prescribed or recommended by psychiatrists (22.5%) followed by general practitioners (12.5%), paediatricians (12.5%) and self-prescriptions (20%). A range of other prescribers were reported including neurologists (7.5%), homeopaths (5%), nutritionists (2.5%), pharmacists (2.5%) and social workers (2.5%).

Following adjusted and unadjusted model logistic regressional analyses, none of the variables analysed were shown to predict psychotropic medication use (*Table 5).* This differed from OTC medications in which unadjusted logistic regressional analysis showed the following variables predicted OTC medication use: income, ethnicity, and Compliant/Calm subscale of the NCBRF (*Table 6).* In the adjusted model only ethnicity predicted OTC medication use. When compared to the white/asian ethnic group, black (O.R = 0.03, 95% C.I 0.0-0.86) or coloured ethnic groupings (O.R =0.09, 95% C.I 0.01-0.62) were less likely to take OTC medications.

Discussion

This study aimed to investigate the prevalence and patterns of medication use in a sample of children and adolescents living with ASD in the South African context. The study findings demonstrate a high prevalence of psychotropic medication use in children with ASD in a South African population. This is consistent with findings from international studies. However, the prevalence rate in this sample was slightly lower (25%) than estimates reported in international samples (30-60%). This sample included school going children only and in South Africa children with severe or profound disabilities are excluded from the education system. Severity of autism has been shown to predict medication use (Rosenberg et al 2010) and it is possible that a sample including lower cognitively functioning children may have shown higher rates of psychotropic medication use. This lower rate may also reflect poorer access to mental and other health care services in South Africa. Types of medications prescribed were similar to previous studies with antipsychotics, antidepressants and stimulants being the most commonly prescribed psychotropics as reported in the international literature. Risperidone was by far the most commonly prescribed agent which may reflect confidence in its FDA approval for use in autism. The atypical antipsychotics are not however without side effects with recent studies showing an increased risk of diabetes in children prescribed these medications (Andrade et al 2011). Five of the ten children taking medications that included risperidone reportedly experienced side effects and in three of the cases the side effects were directly attributed to risperidone. Of the five children who reported weight gain as a side effect of any medication three were taking risperidone, although in two cases this was in combination with other medications. Risperidone was prescribed for a range of other indications beyond its FDA approval including anxiety and mood symptoms and inattention.

The prevalence rates of OTC medications were high (40%) in this sample with 9.2% of the children in the sample taking three or more agents. This finding is also in keeping with international literature. The use of complementary and alternative medicines has been shown to be higher in children with

chronic illnesses and disabilities compared to the general population (Hanson et al 2007). Prevalence rates of 54% for biologically based alternative therapies, such as modified diet and vitamin supplements, have been reported in children with ASD (Hanson et al 2007). There is currently insufficient evidence to support the use of OTC medications or special diets in the treatment of ASD. These medications can be costly. Interestingly income did not predict OTC use but ethnicity did, with the white/asian ethnic group being more likely to take OTC preparations than the black or coloured groups. This may reflect differences in cultural beliefs around OTC medications. Traditional medicines were not specifically asked about in the survey questionnaire. These may not have been considered to be over the counter preparations by participants and may therefore have been underreported.

Response rates to the survey were low in spite of multiple contacts. Survey handouts at the schools received a far better response than the emailed survey request. People may be more likely to complete a survey if they receive a paper copy. Encouragement from staff at the schools may also account for this difference. Medication use in children with ASD is a very sensitive issue and parents may be reluctant to divulge information about medications or OTC preparations that their children are taking. The majority of respondents' children were male (92%). Previous prevalence surveys in the ASD population have also shown a high percentage, usually greater than 80%, of males in the sample. Boys are three to four more times likely to be diagnosed with autism than girls (Steyn and Le Couteur 2003) but this alone does not account for the high percentage of male children in this and other studies. Both schools in this study have a higher proportion of male learners with Alpha School having a male to female learner ratio of 4:1 and Vera School a ratio of 8:1. The higher proportion of male learners may in part explain the higher proportion of male children in this sample.

There are several limitations to this study. The sample was drawn from school going children only and therefore excluded lower functioning children with ASD. There were very few respondents from schools other than those directly targeted and children attending mainstream schools were

therefore also not well represented in the sample. The small sample size may have limited the ability of the study to demonstrate statistical significance of the some of the findings, including behaviour scores predicting medication use. The NCRBF has not been adapted and validated in the South African context. The demographic questionnaire and NCBRF have not been translated into isiXhosa and this may have limited participation of Xhosa speaking participants. Finally, the study was undertaken in a two schools in one province and the findings may not be generalisable to other South African populations.

Notwithstanding the limitations, this pilot study provides an insight into medication use in a South African ASD population and serves as a basis for further research. Larger sample sizes would serve to validate the above findings. As elsewhere, it is important to inform South African health professionals, families and educators, especially those working in low resource settings, of the evidence base for pharmacological treatment and OTC use in children with ASD.

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Tables

Table 1: Demographics of Children in the Study Population																
	Total				Alpha School				Vera School				Other schools			
	N	%	Md	R	N	%	Md	R	N	%	M	SD	N	%	M	SD
Respondents	65	100			23	35.4			36	55.4			6	9.2		
Variables																
Gender																
Male	60	92.3			23	100			31	86.1			6	100		
Female	5	7.7			0	0			5	13.9			0	0		
Age in years			9	5-18			10	5-18			10.9	3.5			8.0	2.8
Ethnicity																
Asian	3	4.6			0	0			3	8.3			0	0		
Black African	10	15.4			6	26.1			2	5.6			2	33.3		
Coloured	27	41.5			15	65.2			10	27.8			2	33.3		
White	25	38.5			2	8.7			21	58.3			2	33.3		
Income																
R501-R2500	10	15.4			8	34.8			1	2.8			1	16.7		
R2501-R6000	12	18.5			8	34.8			4	11.1			0	0		
R6001-R16000	11	16.9			4	17.4			6	16.7			1	33.3		
R16001-R30000	13	20			1	4.3			10	27.8			2	33.3		
R30000+	15	23.1			1	4.3			12	33.3			2	33.3		

Income= Family income per month

M= Mean

Md= Median

SD= Standard deviation

R= Range

Table 2: Physical illness and Physical Medications in Children in the Study Population		
	N	%
Medical illness		
Total	26	40
Epilepsy	5	7.7
Allergic rhinitis	9	13.8
Sinusitis	3	4.6
Asthma	9	13.8
Eczema	2	3.1
Constipation	3	4.6
Hypothyroidism	1	1.5
Cardiac anomaly	1	1.5
Cerebral palsy	1	1.5
Physical Medication		
Total	16	24.6
Lamotrigine	2	3.1
Clobazam	1	1.5
Topiramate	1	1.5
Sodium valproate	3	4.6
Asthavent	4	6.2
Beclomethasone	3	4.6
Nasal spray	2	3.1
Cetirizine	2	3.1
Montelukast	1	1.5
Prednisone	1	1.5
Laxative	3	4.6
Eltroxin	1	1.5

Table 3: Psychotropic Medication Use in Children in the Study Population								
	Total		**Alpha School**		**Vera School**		**Other schools**	
Psychotropic use	N	%	N	%	N	%	N	%
Total psychotropic medication use	16	24.6	2	8.7	10	27.8	4	66.7
Total antipsychotics	11	16.9	2	8.7	7	19.4	2	33.3
Risperidone	10	15.4	2	8.7	6	16.7	2	33.3
Sulpiride	1	1.5	0	0	1	2.8	0	0
Quetiapine	1	1.5	0	0	1	2.8	0	0
Total stimulants	4	6.2	1	4.3	1	2.8	2	33.3
Methylphenidate	4	6.2	1	4.3	1	2.8	2	33.3
Atomoxetine	1	1.5	0	0	0	0	1	16.7
Total antidepressants	4	6.2	0	0	2	5.6	2	33.3
Fluoxetine	2	3.1	0	0	1	2.8	1	16.7
Sertraline	1	1.5	0	0	1	2.8	0	0
Imipramine	1	1.5	0	0	0	0	1	16.7
Total mood stabilisers	2	3.1	0	0	2	5.6	0	0
Lithium	1	1.5	0	0	1	2.8	0	0
Sodium valproate	2	3.1	0	0	2	5.6	0	0
Indication for psychotropics								
Problem behaviour	8	12.3	1	4.3	5	13.9	2	33.3
Inattention and hyperactivity	7	10.8	1	4.3	3	8.3	3	50
Sleep difficulty	2	3.1	1	4.3	1	2.8	0	0
Anxiety	3	4.6	0	0	3	8.3	0	0
Depression	1	1.5	0	0	1	2.8	0	0
Mood stabiliser	2	3.1	0	0	1	2.8	1	16.7
Psychotic symptoms	1	1.5	0	0	1	2.8	0	0

Table 4: Special Diet and Over the Counter medication Use in Children in the Study Population								
	Total		Alpha School		Vera School		Other schools	
Diet and OTC medication use	N	%	N	%	N	%	N	%
Special Diet	10	15.4	3	8.7	7	19.4	1	16.7
Total number of OTC medications	26	40	3	13	20	55.6	3	50
Number of OTC per child								
1	11	16.9	2	8.7	8	22.2	1	16.7
2	9	13.8	0	0	8	22.2	1	16.7
3	3	4.6	1	4.3	2	5.6	0	0
More than 3	3	4.6	0	0	2	5.6	1	16.7
Type of OTC medication								
Multivitamin	12	18.5	3	13	8	22.2	1	16.7
Vitamin C	2	3.1	0	0	2	5.6	0	0
Vitamin B	3	4.6	0	0	3	8.3	0	0
Omega 3 and or 6 all	11	16.9	0	0	9	25	2	33.3
Eye Q (Omega 3 and 6 brand)	6	9.2	0	0	4	11.1	2	33.3
Melatonin	2	3.1	0	0	2	5.6	0	0
Zinc	2	3.1	0	0	1	2.8	1	16.7
Magnesium	3	4.6	0	0	2	5.6	1	16.7
Folic acid	2	3.1	0	0	2	5.6	0	0
Calcium	1	1.5	0	0	1	2.8	0	0
Iron	1	1.5	0	0	0	0	1	16.7
Dietary supplement	5	7.7	0	0	5	13.9	0	0
Probiotics	3	4.6	0	0	2	5.6	1	16.7
Homeopathic preparations	3	4.6	0	0	3	8.3	0	0
Garlic and parsley	1	1.5	0	0	1	2.8	0	0

Table 5: Regressional Analysis of Variables Predicting Psychotropic Medication Use in the Study Population				
	Unadjusted Model		Adjusted Model	
Predictor	**P**	**O.R (95% C.I)**	**P**	**O.R (95% CI)**
School Vera (Reference)		1.0		1.0
School Alpha	0.09	0.24 (0.05-1.26)	0.28	0.05 (0-11.81)
School other	0.08	5.2 (0.82-33)	0.06	1.12 (0.53-2.37)
Age	0.16	1.13 (0.95-1.34)	0.14	1.56 (0.86-295)
Income R0-R15999 (Reference)		1.0		1.0
Income R16000 +	0.71	0.8 (0.24-2.65)	0.07	0 (0-3.08)
Ethnicity White/Asian (Reference)		1.0		1.0
Ethnicity Black	0.15	0.2 (0.02-1.82)	1	0
Ethnicity Coloured	0.16	0.41 (0.12-1.42)	0.17	0 (0-45.89)
NCRBF Behaviour				
Compliant Calm	0.52	0.93 (0.76-1.15)	0.17	0.59 (0.28-1.25)
Adaptive Social	0.6	0.94 (0.74-1.19)	0.86	1.07 (0.49-1.34)
Conduct Problem	0.7	1.02 (0.94-1.09)	0.09	0.81 (0.64-1.03)
Insecure Anxious	0.34	1.04 (0.96-1.12)	0.3	0.81 (0.55-1.2)
Hyperactive	0.1	1.1 (0.98-1.23)	0.09	1.81 (0.9-3.65)
Self Injury Stereotypy	0.44	1.07 (0.9-1.26)	0.14	1.67 (0.85-3.3)
Self Isolated Ritualistic	0.89	1 (0.89-1.15)	0.92	1.02 (0.68-1.52)
Overly Sensitive	0.89	1.01 (0.85-1.21)	0.39	1.46 (0.62-3.44)

O.R = Odds Ratio

C.I = Confidence Interval

Table 6: Regressional Analysis of Variables Predicting OTC Medications in the Study Population				
	Unadjusted Model		Adjusted Model	
Predictor	**P**	**O.R (95% CI)**	**P**	**O.R (95% CI)**
School Vera (Reference)		1.0		1.0
School Alpha	0	0.12 (0.03-0.48)	0.08	0.12 (0.1-1.25)
School other	0.8	0.9 (0.12-4.5)	0.18	9.78 (0.36-264.12)
Age	0.22	1.1 (.94-1.29)	0.98	1.0 (0.78-1.28)
Income R0-R15999 (Reference)		1.0		1.0
Income R16000 +	0.01*	5.25 (1.5-18.38)	0.2	0.17 (0.1-2.57)
NCRBF Behaviour				
Ethnicity White/Asian (Reference)		1.0		1.0
Ethnicity Black	0.01*	0.53 (0.01-0.48)	0.04 *	0.03 (0.0-0.86)
Ethnicity Coloured	0*	0.14 (0.04-0.45)	0.02 *	0.09 (0.01-0.62)
Compliant Calm	0.05*	0.81 (0.66-1.0)	0.71	0.93 (0.63-1.36)
Adaptive Social	0.07	0.81 (0.65-1.02)	0.1	0.64 (0.37-1.09)
Conduct Problem	0.44	1.03 (0.97-1.1)	0.67	0.96 (0.81-1.14)
Insecure Anxious	0.35	1.03 (0.96-1.11)	0.81	1.02 (0.84-1.24)
Hyperactive	0.1	1.09 (0.99-1.2)	0.65	1.06 (0.82-1.36)
Self injury Stereotypy	0.42	1.07 (0.91-1.24)	0.84	0.97 (0.69-1.36)
Self isolated Ritualistic	0.4	1.05 (0.94-1.18)	0.87	0.98 (0.74-1.29)
Overly Sensitive	0.19	1.11 (0.94-1.31)	0.2	1.3 (0.87-2)

* Statistically significant difference at P ≤ 0.05

O.R=Odds Ratio

C.I = Confidence Interval

Part D: Supporting Documents

1. Nisonger Child Behaviour Rating Form Score Sheet

THE NISONGER CHILD BEHAVIOR RATING FORM

PARENT VERSION: SCORE SHEET

Child's Name: _____ Child's Date of Birth: ____/____/____
month day year

Rater's Name: _____ Date of Rating: ____/____/____
month day year

Relation of Rater to Child: • parent [1] • other [9]: _____
(please specify)

INSTRUCTIONS. Transcribe the ratings from the Nisonger CBRF and write them into the "rating" column next to the appropriate item number "#". When all ratings have been transcribed, total the columns to obtain the subscale scores.

II. POSITIVE SOCIAL **III. PROBLEM BEHAVIOR**

Compliant / Calm		Adaptive Social		Conduct Problem		Insecure / Anxious		Hyperactive		Self-Injury / Stereotypic		Self-Isolated / Ritualistic		Overly Sensitive	
#	rating	#	rating	#	rating	#	rating	#	rating	#	rating	#	rating	#	rating
1		2		2		16		9		6		1		3	
3		5		4		21		13		11		18		5	
4		7		7		23		19		22		25		14	
6		8		8		30		24		32		29		15	
9		Total ____		10		31		33		43		37		20	
10				12		34		35		53		47		Total ____	
Total ____				17		41		38		58		49			
				26		42		39		Total ____		64			
				36		44		46				Total ____			
				40		45		Total ____							
				50		48									
				54		52									
				56		55									
				57		60									
				63		65									
				66		Total ____									
				Total ____											

Developed by M. G. Aman, M. J. Tassé, J. Rojahn, and D. Hammer, 1995.

2. Faculty Research Ethics Committee Approval Letter

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

06 October 2009

REC REF: 416/2009

Dr K Louw
Psychiatry

Dear Dr Louw

PROJECT TITLE: PREVALENCE AND PATTERNS OF MEDICATION USE IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDERS IN THE WESTERN CAPE.

Thank you for submitting your study to the Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th October 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

S Thomas

3. Aim and Scope

Journal of Child and Adolescent Mental Health

Journal Details

Journal of Child & Adolescent Mental Health

Published By: Routledge
Volume Number: 23
Frequency: 2 issues per year
Print ISSN: 1728-0583
Online ISSN: 1728-0591

Aims & Scope

The ***Journal of Child & Adolescent Mental Health*** publishes papers that contribute to improving the mental health of children and adolescents, especially those in Africa.

Papers from all disciplines are welcome. It covers subjects such as epidemiology, mental health prevention and promotion, psychotherapy, pharmacotherapy, policy and risk behaviour.
The journal contains review articles, original research (including brief reports), clinical papers in a 'Clinical perspectives' section and book reviews.

The Journal is published in association with the South African Association for Child and Adolescent Psychiatry and Allied Professions (SAACAPAP). The SAACAPAP is the professional body for child and adolescent mental health practitioners in South Africa. It was initiated in 1978, and since then has been an active member of the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP).

Additional information about the society can be obtained from:

The General Secretary
SAACAPAP
PO Box 13031
Mowbray 7505
South Africa

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Journal of Child and Adolescent Mental Health

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Population Reference Bureau (2002) Untitled fact sheet. Available at: http://www.prb.org/content/navigationMenu/Other_reports /2000-2002/sheet1.html. [Accessed 22 February 2002]

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